Protocol Title:	A randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, pharmacokinetics, pharmacodynamics, safety and immunogenicity of MB09 (proposed denosumab biosimilar) versus Prolia® (EU-sourced) in postmenopausal women with osteoporosis (SIMBA Study)
NCT Number:	NCT05338086
Protocol version date:	Version 2.0, 07 November 2022

[redacted]

CLINICAL STUDY PROTOCOL
MB09-C-01-19
EudraCT 2021-003609-24

A randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, pharmacokinetics, pharmacodynamics, safety and immunogenicity of MB09 (proposed denosumab biosimilar) versus Prolia® (EU-sourced) in postmenopausal women with osteoporosis (SIMBA Study)

(A study to compare efficacy, pharmacokinetics, pharmacodynamics, safety and immunogenicity of MB09 [proposed denosumab biosimilar] to Prolia® [EU-sourced] in postmenopausal osteoporosis [SIMBA Study])

[redacted]

Title Page

MB09-C-01-19

Sponsor:	mAbxience c/Manuel Pombo Angulo 28 3rd Floor 28050 Madrid Spain
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Version of Protocol:	Version 2.0 (Amendment 1)
Date of Protocol:	07 November 2022
Compound Name:	MB09
Study Phase:	Interventional

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, pharmacokinetics, pharmacodynamics, safety and immunogenicity of MB09 (proposed denosumab biosimilar) versus Prolia® (EU-sourced) in postmenopausal women with osteoporosis (SIMBA Study)
Protocol Number	MB09-C-01-19
Protocol Date and Version	07 November 2022, Version 2.0 (Amendment 1)

Protocol accepted and approved by:

[redacted]

mAbxience

[redacted]

Signature

[redacted]

mAbxience

[redacted]

Signature

[redacted]

[redacted]

Signature

Protocol Approval – Lead Statistician

Study Title	A randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, pharmacokinetics, pharmacodynamics, safety and immunogenicity of MB09 (proposed denosumab biosimilar) versus Prolia® (EU-sourced) in postmenopausal women with osteoporosis (SIMBA Study)
Protocol Number	MB09-C-01-19
Protocol Date and Version	07 November 2022, Version 2.0 (Amendment 1)

Protocol accepted and approved by:

Lead Statistician

PPD

Signature

Protocol Approval – Medical Monitor

Study Title	A randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, pharmacokinetics, pharmacodynamics, safety and immunogenicity of MB09 (proposed denosumab biosimilar) versus Prolia® (EU-sourced) in postmenopausal women with osteoporosis (SIMBA Study)
Protocol Number	MB09-C-01-19
Protocol Date and Version	07 November 2022, Version 2.0 (Amendment 1)

Protocol accepted and approved by:

Medical Monitor

[redacted]
PPD Serbia
[redacted]

[redacted]

_____
Signature

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, pharmacokinetics, pharmacodynamics, safety and immunogenicity of MB09 (proposed denosumab biosimilar) versus Prolia® (EU-sourced) in postmenopausal women with osteoporosis (SIMBA Study)" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with Version 2.0 (Amendment 1), dated 07 November 2022, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with mAbxience or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a subinvestigator.

My site has implemented risk minimisation and the mitigation plan for COVID-19 in line with local regulations and best practices, including precautions such as use of personal protective equipment for subjects, site staff and visitors, site staff health checks and the disinfection of site premises.

I will not supply the study drug to any person not authorised to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications. I will not disclose information regarding this clinical investigation or publish results of the investigation without authorisation from mAbxience.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

Protocol Amendment Summary of Changes

Protocol Version History	
Protocol Version	**Date**
Version 2.0 (Amendment 1)	07 November 2022
Original Protocol	30 September 2021

Amendment 1 (07 November 2022)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC and Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment: Amendment 1 has been issued to incorporate changes validated by clarification letters, correction of typos and to better explain the reasons for discontinuations of treatment.

Major changes from Original Protocol (30 September 2021) to Amendment 1 (07 November 2022) are summarized in the table overleaf. Additional minor changes to the protocol and changes to the synopsis are not listed but were applied, as applicable.

Section # and Name	Description of Change	Brief Rationale
Title Page Sponsor Signatory	Changed sponsor medical advisors.	Administrative change.
Synopsis (Study Design) 3.1 Study Design	Clarified that dual-energy X-ray absorptiometry (DXA) scan will be valid for up to 3 months for screening evaluation.	According to the Osteoporosis Management Guidelines in Postmenopausal Women (Eastell et al 2019), it is recommended that repeat bone mineral density measurements by DXA after an interval of 1 to 3 years may be considered to assess response to treatment in postmenopausal women with a low bone mineral density and at high risk of fractures who are being treated for osteoporosis. Due to the short time that 3 months represents in bone metabolism, the recommendations for the management of osteoporosis in postmenopausal women and to limit radiation exposure, the validity time of the screening DXA scan has been updated to 3 months.
Table 13-1 Schedule of Events (Footnotes f and p) 13.3.1 Benefit and Risk Assessment on Study Population 13.3.2.3 Rescheduling of Visit and Study Drug Administration Schedule of Subjects	Clarified that DXA scan will be valid for up to 3 months for screening evaluation, provided the investigator considers the data from the DXA scan to be relevant (ie, the same DXA instrument will be used for the study and data on total hip, femoral neck and lumbar spine are available). In the event the investigator deems the DXA scan invalid, a repeat DXA scan should be performed for the subject who has been re-examined.	
Synopsis (Study Design) 3.1 Study Design 5.1 Method of Assigning Subjects to Treatment Arms 7.5 Description of Subgroups to be Analysed	Edits done to clarify the upper age limit of 80 years in the stratification for randomization and subgroup analyses.	Change from <80 to ≤80 years to include the age cutoff.
Synopsis (Diagnosis and Criteria for Inclusion and Exclusion) 4.1.1 Inclusion Criteria (#3)	Clarified that Inclusion Criterion #3 is based on age rounded down to the nearest year.	Clarification change.
Synopsis (Diagnosis and Criteria for Inclusion and Exclusion) Synopsis (Combination Treatment) 4.1.1 Inclusion Criteria (#7) 4.1.2 Exclusion Criteria (#6) 5.2.2 Co-Administration of Calcium and Vitamin D	Updated “calcium” measurement to “albumin-adjusted total serum calcium” measurement.	Clarification change.

Section # and Name	Description of Change	Brief Rationale
5.2.2.1 Managing Hypercalcaemia and Hypocalcaemia 6.5.2 Clinical Safety Laboratory Assessments Table 13-1 Schedule of Events (Footnote m)		
Synopsis (Diagnosis and Criteria for Inclusion and Exclusion) 4.1.2 Exclusion Criteria (#6)	In Exclusion Criterion #6, added thyroid stimulating hormone level (<0.1 µU/mL) for subclinical hyperthyroidism.	Addition of a cutoff for the thyroid stimulating hormone level to define the threshold of subclinical hyperthyroidism.
Synopsis (Diagnosis and Criteria for Inclusion and Exclusion) 4.1.2 Exclusion Criteria (#12) 5.9 Prohibited Concomitant Therapy Table 5-1 Summary of Prohibited Medications With Washout Periods	Correction of the typo of 'eg' to clarify that the only antiplatelet therapy considered prohibited is clopidogrel and that other antiplatelet drugs are allowed.	Clarification change.
4.2.1 Discontinuation From Study Drug	For subjects who are discontinued from study drug because they were dosed in error despite not meeting eligibility criteria, it was clarified that subjects with osteoporosis and no safety concerns and with potential clinical benefit may continue in the study as per principal investigator's discretion.	Clarification change to allow subjects with osteoporosis to continue in the trial if the principal investigator considers that there is a potential clinical benefit and no safety concern.
4.3.2 Reasons for the Investigator to Withdraw the Subject	For the statement "A subject who does not meet the protocol-defined eligibility criteria should not proceed in the study except for the 6-month safety follow-up", the following exception was added: *with the exception of subjects with osteoporosis and dosed in error because they did not meet the eligibility criteria of the study but without safety concerns and with potential clinical benefit in the opinion of the PI, as those may continue in the study as per investigator discretion.*	Clarification change.

Section # and Name	Description of Change	Brief Rationale
Synopsis (Combination Treatment) 5.2.2 Co-Administration of Calcium and Vitamin D	Clarified that ergocalciferol is the preferable supplement (for at least 2 weeks), although any other vitamin D supplement can be used according to the local clinical practice.	Correction of erred text that restricted the site's choice of Vitamin D supplementation.
6.1.2 Screening Bone Mineral Density Assessment	Clarified the screening period duration for DXA scans of the lumbar spine (changed from "up to 28 days prior to the beginning of the Screening Period" to "up to 3 months for the Screening evaluation".)	Inclusion of change already documented as per clarification letter.
6.1.2 Screening Bone Mineral Density Assessment	Removed the text that DXA scan images obtained as part of the routine standard of care can be used for screening.	Removal of the text allowing local DXA scans to be used in screening as only central vendor scans would serve as eligibility scans to ensure standardization in the technical quality of the images and in the reports.
6.5.6.2 Injection Site Reaction Monitoring	Clarified that injection site reaction details will be recorded in the source documents, and severity (worst grade over categories of pain, tenderness, erythema and swelling) would also be collected in the electronic case report form (eCRF) as an AESI.	Correction of ambiguity in the parameter to be collected in the eCRF.
6.5.6.3 Hypersensitivity/Allergic Reaction Monitoring	Clarified that the subject should be permanently discontinued from the study drug and should be asked to complete the scheduled visits until the end of the Main Treatment Period at Month 12.	Correction in the text to remove "withdrawn from study" and made consistent with the intent in other parts of the protocol.
7.5 Description of Subgroups to be Analysed	Corrected the upper limit of body weight in line with the inclusion criteria. (from <99.9 to ≤99.9 kg)	Typo correction to add equality for consistency across the protocol.
Table 7-2 Summary of Statistical Methods, Including Sensitivity Analyses	Removed "(2a) lumbar spine BMD after 6 months" from Estimand 3a-4a.	Correction of typo as the removed text corresponds to another section.
7.6.8.1 Adverse Events	Clarification of wording to reflect injection site reactions will be summarised by severity (worst graded sign or symptom).	Clarification change.
Table 13-1 Schedule of Events (Footnote s)	Clarified that samples for immunogenicity testing will be collected up to 30 minutes prior to dosing of the study	Clarification change.

Section # and Name	Description of Change	Brief Rationale
	drug. Other samples may be taken at any time during a scheduled visit.	

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Protocol Synopsis

Protocol Number: MB09-C-01-19

Title: A randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, pharmacokinetics, pharmacodynamics, safety and immunogenicity of MB09 (proposed denosumab biosimilar) versus Prolia® (EU-sourced) in postmenopausal women with osteoporosis (SIMBA Study)

Short Title: A study to compare efficacy, pharmacokinetics, pharmacodynamics, safety and immunogenicity of MB09 (proposed denosumab biosimilar) to Prolia® (EU-sourced) in postmenopausal women (SIMBA Study)

Sponsor: mAbxience

Study Phase: Interventional

Study Sites: Approximately 60 sites in Europe and Latin America. In Europe, the study is planned to be conducted in Ukraine, Poland, Czech Republic, Bulgaria, Serbia, Estonia, Georgia and Latvia. In Latin America, the study is planned to be conducted in Mexico. Note: Additional sites or countries may be included in the study.

Indication: Postmenopausal women diagnosed with osteoporosis

Rationale:

This multicentre, multinational global comparative efficacy study (MB09-C-01-19) will be conducted as part of a clinical development programme and will assess the therapeutic equivalence in efficacy, safety, PK, PD, and immunogenicity of MB09 compared to EU-sourced Prolia® (EU-Prolia). After collecting the totality of evidence proving its biosimilarity to Prolia, MB09 may provide an opportunity to improve access to treatment while delivering substantial cost savings.

The design of this study takes into account the EU Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies: Non-Clinical and Clinical (EMEA/CHMP/BMWP/403543/2010; 30 May 2012), PMDA Guideline on the Quality, Safety and Efficacy Assurance of Follow-on Biologics (PFSB/ELD Notification No 0304007

04 March 2009) and the FDA Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015).

Objectives, Estimands and Endpoints:

The primary objective, endpoint and estimands are presented in the table below and will be studied in the Main Treatment Period.

Primary Objective	Endpoint and Estimand Descriptions
To demonstrate equivalent efficacy of MB09 to EU-Prolia in postmenopausal women with osteoporosis in terms of lumbar spine BMD at Month 12.	**Endpoint:** Percentage change from baseline (%CfB) in lumbar spine BMD after 52 weeks.
	Estimand 1a (Primary): Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive two denosumab doses without any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications.
	Estimand 1b (Supportive): Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any prohibited therapies or other osteoporosis medications are taken.

[1] Women will not have been previously treated with denosumab but may have had prior treatment with bisphosphonates and will be co-administered calcium and vitamin D supplements.

Abbreviations: %CfB, percentage change from baseline; BMD, bone mineral density; EU-Prolia, EU-sourced Prolia.

Note: The screening BMD assessment will be taken as the baseline BMD assessment.

The key secondary objectives with estimands are presented in the table below for the Main Treatment Period.

Secondary Objectives	Estimand Description (Including *Endpoint*)
To assess the efficacy of MB09 to EU-Prolia in postmenopausal women with osteoporosis in terms of lumbar spine BMD at Month 6, and hip and femur neck BMD at Month 6 and Month 12.	**Estimand 2a\3a\4a:** Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB (zero is taken for anyone who dies) in* • *(2a) lumbar spine BMD after 6 months.* • *(3a) hip BMD after 6 and 12 months.* • *(4a) femur neck BMD after 6 and 12 months.* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive scheduled denosumab dose(s) without any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications. **Estimand 2b\3b\4b:** Same as Estimand 1b for each endpoint above irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any prohibited therapies or other osteoporosis medications are taken.
To assess the PD profile of MB09 to EU-Prolia in postmenopausal women with osteoporosis in terms of sCTX AUEC up to Month 6 and sCTX at Month 12.	**Estimand 5:** Ratio of geometric means (MB09/EU-Prolia) in *$sCTX\ AUEC_{0\text{-}6\ months}$* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming all women receive their first denosumab dose without any errors in dosing and without receipt of any prohibited therapies or other osteoporosis medications up to 6 months after first dose. **Additional summary:** Mean difference in sCTX at 11 days; 1, 3 and 6 months after the first dose; and 6 months after the second dose of study drug.

[1] Women will not have been previously treated with denosumab but may have had prior treatment with bisphosphonates and will be co-administered calcium and vitamin D supplements.

Abbreviations: %CfB, percentage change from baseline; AUEC, area under the effect curve; $AUEC_{0\text{-}6\ months}$, area under the effect curve from zero to 6 months; BMD, bone mineral density; EU-Prolia, EU-sourced Prolia; PD, pharmacodynamic; sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen.

Note: The screening BMD assessment will be taken as the baseline BMD assessment.

Other secondary objectives and endpoints for the Main Treatment Period are presented in the table below.

Secondary Objectives	***Endpoints***
To assess the PK profile of MB09 compared with EU-Prolia.	• *$AUC_{0\text{-}6\ months}$ and C_{max} following the first dose.* • *C_{trough} of serum denosumab at Month 6 and Month 12.*
To evaluate the safety profile of MB09 compared with EU-Prolia.	• *Subject incidence of treatment-emergent adverse events up to and including Month 12.* • *Subject incidence of adverse events of special interest (injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction and atypical femoral fracture) up to and including Month 12.* • *Subject incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG and vital signs from baseline and up to and including Month 12.* • *Subject incidence of deaths and serious adverse events up to Month 12.*
To assess the immunogenicity of MB09 compared with EU-Prolia assessed through antidrug antibodies.	• *Binding and neutralising serum denosumab antibodies from baseline and up to and including Month 12.*

Abbreviations: $AUC_{0\text{-}6\ months}$, area under the concentration-time curve from zero to 6 months; C_{max}, observed maximum serum concentration after administration; C_{trough}, trough (predose) serum concentration; ECG, electrocardiogram; EU-Prolia, EU-sourced Prolia; PK, pharmacokinetic.

The key secondary objectives and endpoints are presented in the table below for the Transition/Safety Follow-Up Period.

Secondary Objectives	***Endpoints***
To assess the PK profile: i. after the single transition from EU-Prolia to MB09 ii. on MB09 throughout each compared with those on EU-Prolia throughout.	• *Transition Period $AUC_{0\text{-}6\ months}$ and C_{max} following the third dose at Month 12.* • *C_{trough} of serum denosumab at Transition Period Month 6.*
To assess the PD profile: i. after the single transition from EU-Prolia to MB09 ii. on MB09 throughout each compared with those on EU-Prolia throughout.	• *Transition Period sCTX AUEC up to Transition Period Month 6.* • *C_{trough} of sCTX at Month 12 and Transition Period Month 6.*
To assess the risk of hypersensitivity and adverse events: i. after the single transition from EU-Prolia to MB09 ii. on MB09 throughout each compared with those on EU-Prolia throughout.	• *Subject incidence of treatment-emergent adverse events from third dose at Month 12 and up to and including Transition Period Month 6.* • *Subject incidence of adverse events of special interest (injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction and atypical femoral fracture) from third dose at Month 12 and up to and including Transition Period Month 6.* • *Subject incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG and vital signs from third dose at Month 12 and up to and including Transition Period Month 6.* • *Subject incidence of deaths and serious adverse events from third dose at Month 12 and up to and including Transition Period Month 6.*
To assess the risk of immunogenicity through formation of antidrug antibodies: i. after the single transition from EU-Prolia to MB09 ii. on MB09 throughout each compared with those on EU-Prolia throughout.	• *Binding and neutralising serum denosumab antibodies from Month 12 and up to and including Transition Period Month 6.*

Abbreviations: $AUC_{0\text{-}6\ months}$, area under the concentration-time curve from zero to 6 months; AUEC, area under the effect curve; C_{max}, observed maximum serum concentration after administration; C_{trough}, trough (predose) serum concentration; ECG, electrocardiogram; EU-Prolia, EU-sourced Prolia; PD, pharmacodynamic; PK, pharmacokinetic; sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen.

Diagnosis and Criteria for Inclusion and Exclusion:

Each subject must meet all of the following criteria to be enrolled in this study:

1. Signed informed consent must be obtained prior to participation in the study.
2. Postmenopausal women. Postmenopausal status is defined as at least 12 consecutive months of amenorrhea prior to date of screening with a follicle-stimulating hormone level of ≥30 mIU/mL or surgical menopause (bilateral oophorectomy with or without hysterectomy) ≥12 months prior to the screening visit when follicle-stimulating hormone is not required.
3. Aged ≥55 and ≤80 years at screening (based on age rounded down to the nearest year).
4. Body weight ≥50 kg and ≤99.9 kg, and a body mass index of ≤30 kg/m^2 at screening.
5. Absolute BMD consistent with T-score ≤-2.5 and ≥-4 at the lumbar spine or total hip as measured by DXA during the Screening Period.
6. At least two intact, nonfractured vertebrae in the L1 to L4 region (vertebrae to be assessed by central reading of lateral spine X-ray during the Screening Period) and at least one hip joint is evaluable by DXA.
7. Adequate organ function as defined by the following criteria:
   - Normal levels of vitamin D (≥20 to ≤64 ng/mL) and albumin-adjusted total serum calcium (≥8.5 to ≤10.5 mg/dL) at screening.
   - Serum aspartate aminotransferase, alanine aminotransferase and bilirubin ≤2.0 × ULN in the absence of any evidence of viral hepatitis.
   - Platelets ≥100 × 10^9/L.
   - Haemoglobin ≥9.0 g/dL.
   - Albumin 3.4 to 5.4 g/dL.
   - Glomerular filtration rate >30 mL/min.
   - Adequate coagulation parameters such as: INR ≤2.0 and aPTT ≤1.5 × ULN.

Subjects meeting any of the following criteria will be excluded from the study:

1. Previous exposure to denosumab (Prolia, Xgeva®, or denosumab biosimilar) or any other monoclonal antibody (eg, romosozumab) or fusion protein containing IgG or other biologic agent targeting IgG.
2. Confirmed or suspected with SARS-CoV-2 (COVID-19) at screening or has been diagnosed with COVID-19 or had contact with a COVID-19 infected patient within 14 days of screening. Note: Subjects who have a COVID-19 infection will be allowed to be rescreened if they have a confirmatory negative COVID-19 test result and have completely recovered from COVID-19 before being entered into the study.
3. Height, weight or girth that may preclude accurate DXA measurements.
4. History and/or presence of one severe or more than two moderate vertebral fractures or hip fracture (as determined from the subject's medical history or by the central imaging centre during the Screening Period). Note: All subjects will have an X-ray performed at screening and this radiograph will be used as the reference radiograph that all radiographs performed during the study will be compared to.
5. Recent long bone fracture (within 6 months). Presence of active healing fracture according to assessment of investigators.
6. History and/or presence of bone metastases, bone disease, or metabolic disease other than osteoporosis, which could interfere with the interpretation of the findings, eg, osteogenesis imperfecta, osteopetrosis, osteomalacia, rheumatoid arthritis, Paget's disease, ankylosing spondylitis, Cushing's disease, hyperprolactinemia, malabsorption syndrome, hypoparathyroidism or hyperparathyroidism (irrespective of current controlled or uncontrolled status), hypocalcaemia or hypercalcaemia (based on albumin-adjusted total serum calcium). Current hyperthyroidism or hypothyroidism are not allowed unless they are well-controlled with stable therapy for at least 3 months prior to baseline and no change of start of therapy for hyperthyroidism or hypothyroidism is anticipated during the study. Subclinical hyperthyroidism (thyroid-stimulating hormone levels <0.1 μU/mL) due to its effect on bone metabolism is not allowed.
7. Malignancy within the 5 years before enrolment (except cervical carcinoma in situ or basal cell carcinoma, which are not prohibitive).
8. Drugs being investigated for osteoporosis.
9. Intravenous bisphosphonate, strontium or fluoride administered for osteoporosis within 5 years of screening.
10. Oral bisphosphonates ≥12 months cumulative use prior to screening. If used

<12 months cumulatively and the last dose was ≥12 months before screening, the subject can be enrolled.

11. Ongoing use of any osteoporosis treatment (excluding calcium and vitamin D supplements) taken within the past 5 years prior to screening, with the exception of the medications listed below that are required to adhere to rules for the following washout periods:
    - Tibolone, oestrogen/progesterone containing products including any oestrogen/progesterone contraceptives or hormone-replacement therapy, selective oestrogen receptor modulators, received within 3 months prior to screening.
    - Calcitonin, calcitriol, maxacalcitol, falecalcitriol, or alfacalcidol: dose received within 3 months prior to screening.
    - Cinacalcet: dose received within 3 months prior to screening.
    - Parathyroid hormone or parathyroid hormone derivatives within the last 3 months before initial administration of the study drug.
12. Other bone active drugs including heparin, warfarin, antiplatelet therapy (clopidogrel), anticonvulsives (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin-releasing hormone agonists, anabolic steroids, aluminium, aromatase inhibitors, protease inhibitors, methotrexate, and thiazolidinediones within the past 3 months before initial administration of the study drug. Note: Direct oral anticoagulants are allowed as they have no effect on bone metabolism.
13. Systemic glucocorticosteroids (≥5 mg prednisone equivalent per day for ≥10 days or a total cumulative dose of ≥50 mg) within the past 3 months before screening.
14. Use of certain immunosuppressants (eg, calmodulin and calcineurin inhibitors) within the past 3 months prior to screening.
15. Chronic treatment of protein pump inhibitors if used continuously for longer than a year within the past 3 months prior to screening.
16. Use of other investigational drugs within five half-lives of the drug or until the expected PD effect of the drug has returned to baseline or within 30 days prior to screening, whichever is longer, or longer if required by local regulations.
17. Oral or dental conditions: osteomyelitis or history and/or presence of osteonecrosis of the jaw, presence of risk factors for osteonecrosis of the jaw (eg, periodontal disease, poorly fitting dentures, invasive dental procedures such as tooth extractions in 6 months before screening), active dental or jaw condition which requires oral

surgery and/or planned invasive dental procedure at the discretion of the investigator. Note: Subjects may be further examined by a dental specialist at the investigator's discretion.

18. Vitamin D deficiency (25-OH vitamin D serum level <20 ng/mL). Vitamin D repletion is permitted at the investigator's discretion and subjects will be rescreened to re-evaluate vitamin D level post repletion. Vitamin D levels will be re-tested once within the Screening Period.
19. Known intolerance to, or malabsorption of calcium or vitamin D supplements.
20. History and/or presence of a severe allergic reaction (eg, general anaphylaxis).
21. Has an active infection that required the use of oral antibiotics within 2 weeks or parenteral antibiotics used within 4 weeks prior to randomisation. Has an HBV, HCV, HIV-1/HIV-2 or SARS-CoV-2 positive test result at screening. If a positive test result is obtained, a confirmatory test is required.
22. Received a COVID-19 vaccine within 14 days prior to randomisation to study drug or is planning to receive a COVID-19 vaccine within 14 days prior to study drug administration at Month 6 or Month 12.
23. History and/or presence of significant cardiac disease as per investigator's discretion, including but not restricted to: ECG abnormalities at screening indicating significant risk of safety for subjects participating in the study, history and/or presence of myocardial infarction within 6 months before screening, history and/or presence of NYHA class III or IV heart failure, any unstable pulmonary disease (eg, chronic obstructive disease), hematologic, neurological, psychiatric, endocrine (eg, diabetes), autoimmune disease (eg, Crohn's disease or coeliac disease), gastrointestinal, renal, urinary, skeletal, or dermatologic disease which can be judged as clinically significant at the investigator's discretion.
24. Subject has a history or current evidence of any condition, therapy, laboratory abnormality or other circumstances that might, in the opinion of the investigator, confound the results of the study, interfere with the subject's ability to comply with the study procedure, or make participation in the study not in the subject's best interest.
25. Currently abuses alcohol or drugs or has a history of alcohol or drug abuse within 12 months prior to the first administration of the study drug.
26. Have major surgery (including surgery to bone), or significant traumatic injury occurring within 4 weeks before randomisation or if one is planned during the study.
27. Have immobility due to severe or chronically disabling conditions.

Study Design:

This is a randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, PK, PD, safety and immunogenicity of MB09 (proposed denosumab biosimilar) and EU-Prolia in postmenopausal women with osteoporosis.

The study will randomise approximately 528 postmenopausal women with osteoporosis aged ≥55 and ≤80 years old with a BMD consistent with T-score of ≤ -2.5 and ≥ -4 at the lumbar spine or hip as measured by DXA during the Screening Period. Screening evaluations will be completed within 28 days prior to randomisation with the exception of the DXA scan, which would be valid for up to 3 months.

On Day 1, 528 eligible postmenopausal women with osteoporosis will be randomised in a 2:1:1 ratio to receive MB09-MB09 (Arm 1), Prolia-MB09 (Arm 2) or Prolia-Prolia (Arm 3) using an IRT system.

The randomisation will be stratified by baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 SD), body mass index (<25 and ≥25 kg/m^2), age at study entry (≥55 to <68 years versus ≥68 to ≤80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use).

During the Main Treatment Period, subjects will receive one subcutaneous injection (60 mg/mL) of study drug on Day 1 and at Month 6. At Month 12, after all efficacy and safety assessments have been performed, the subject will enter the Transition/Safety Follow-up Period and will receive the third dose of study drug. Subjects assigned to the MB09MB09 arm (Arm 1) will receive MB09 on Day 1, at Month 6 and at Month 12. Subjects assigned to the ProliaMB09 arm (Arm 2) will receive EU-Prolia on Day 1 and at Month 6, and MB09 at Month 12. Subjects assigned to the Prolia-Prolia arm (Arm 3) will receive EU-Prolia on Day 1, at Month 6 and at Month 12. All subjects will be followed up to Transition Period Month 6.

The study visits are as follows:

- Visit 1: Screening (-28 days to -1 day)
- Visit 2: Baseline (Day 1) (Main Treatment Period): First administration of study drug

- Visit 3: Day 11 (Main Treatment Period)
- Visit 4: Month 1 (Main Treatment Period)
- Visit 5: Month 3 (Main Treatment Period)
- Visit 6: Month 6 (Main Treatment Period): Second administration of study drug
- Visit 7: Month 9 (Main Treatment Period)
- Visit 8: Month 12 (Main Treatment Period and Transition/Safety Follow-Up Period): Third administration of study drug
- Visit 9: Month 12 + 10 days (Transition Period Day 11)
- Visit 10: Month 12 + 5 weeks (Transition Period Month 1)
- Visit 11: Month 15 (Transition Period Month 3)
- Visit 12: Month 18 (Transition Period Month 6)

The End of Treatment visit will be at Month 12 (ie, subjects will receive the third dose of study drug). The End of Study visit will be performed at Month 18 (Transition Period Month 6) for subjects who receive the third dose of study drug at Month 12. Subjects who have the last study drug dose on Day 1 or Month 6 will have their last visit at Month 12.

Duration of Treatment:

Enrolment of subjects will continue until approximately 528 subjects have been randomised to treatment. The study will be completed when the last subject completes the End of Study visit or withdraws early from the study.

The maximum study duration for a subject will be approximately 19 months: 28 days for screening, a Main Treatment Period of 12 months, and a Transition/Safety Follow-Up Period of 6 months (Transition Period Month 6).

Efficacy Assessments:

An independent radiology review committee will assess the BMD (primary efficacy endpoint: %CfB to Month 12 in BMD) using DXA at Month 6 and Month 12.

Pharmacokinetic Assessments for the Main Treatment Period:

Blood samples for measuring serum concentrations of denosumab will be collected at Day 1 (0 predose), Day 11, Month 1, Month 3, Month 6 (predose) and Month 12 (for those subjects entering the Transition Period, this sample should be taken prior to the third dose of study drug).

Pharmacokinetic Assessments for the Transition/Safety Follow-Up Period:

Blood samples for measuring serum concentrations of denosumab collected at Month 12 (predose) and 10 days, 5 weeks, 3 months and 6 months after the administration of the third dose of study drug (ie, Transition Period Day 11, Transition Period Month 1, Transition Period Month 3 and Transition Period Month 6).

Pharmacodynamic Assessments for the Main Treatment Period:

Blood samples for measuring concentrations of sCTX will be collected on Day 1 (0 predose), Day 11, Month 1, Month 3, Month 6 (predose) and Month 12 (for those subjects entering the Transition Period, this sample should be taken prior to the third dose of study drug).

Pharmacodynamic Assessments for the Transition/Safety Follow-Up Period:

The PD samples for measuring concentrations of sCTX will be collected at Month 12 (predose) and 10 days, 5 weeks, 3 months and 6 months after the administration of the third dose of study drug (ie, Transition Period Day 11, Transition Period Month 1, Transition Period Month 3 and Transition Period Month 6).

Immunogenicity Assessments for the Main Treatment Period:

During the Main Treatment Period, all subjects will undergo blood sampling for the assessment of antidrug antibody to denosumab (binding and neutralising). Antidrug antibodies to denosumab will be assessed at the following time points: Day 1 (0 predose),

Day 11, Month 1, Month 3, Month 6 (predose) and Month 12 (for those subjects entering the Transition Period, this sample should be taken prior to the third dose of study drug).

Immunogenicity Assessments for the Transition/Safety Follow-Up Period:

During the Transition/Safety Follow-Up Period, all subjects will undergo blood sampling for the assessment of antidrug antibody to denosumab (binding and neutralising). Antidrug antibodies to denosumab will be assessed at Month 12 (predose) and 10 days, 5 weeks, 3 months and 6 months after the administration of the third dose of study drug (ie, Transition Period Day 11, Transition Period Month 1, Transition Period Month 3 and Transition Period Month 6).

Safety Assessments:

Safety assessments will be performed on adverse events (including serious adverse events), adverse events of special interest (injection site reaction, drug-related hypersensitivity/allergic reaction monitoring, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction and atypical femoral fracture), vital sign assessments, body weight, height, body mass index, lateral spine radiography (screening only; radiographs will be performed as required for suspected new clinical fractures), ECG, physical examination, clinical laboratory analyses and prior and concomitant medications.

Adverse events will be documented during the whole study. Adverse events will be rated using the CTCAE grading criteria Version 5.0 (Grade 1 to Grade 5). The severity of pain, tenderness, erythema and induration/swelling at the injection site will be assessed up to 1 hour (±10 minutes) after the End of Study drug administration.

Details of Applicable Monitoring Committee:

This study will be monitored by a committee of independent experts consisting of a PK specialist, statistician, chairing physician and independent physician. The DSMB will review and evaluate accumulating unblinded safety data to ensure the safety of study subjects and also review study results. The DSMB will communicate safety concerns and recommendations regarding study modifications or termination to mAbxience at any time during the conduct of the study. This decision will be based on benefit-risk evaluation.

Records of all meetings will be archived. Further details will be provided in the independent DSMB charter.

Study Drug, Dosage, and Route of Administration:

Proposed Denosumab Biosimilar Drug (MB09)

Pre-filled syringe containing 60 mg/mL solution for subcutaneous use, one administration per dose.
MB09 has the same formulation as EU-Prolia:
Acetic acid, glacial*
Sodium hydroxide (for pH adjustment)*
Sorbitol (E420)
Polysorbate 20
Water for injection
*Acetate buffer is formed by mixing acetic acid with sodium hydroxide

Reference Medicinal Product EU-Prolia

Pre-filled syringe containing 60 mg/mL solution for subcutaneous use, one administration per dose.
EU-Prolia formulation:
Acetic acid, glacial*
Sodium hydroxide (for pH adjustment)*
Sorbitol (E420)
Polysorbate 20
Water for injection

*Acetate buffer is formed by mixing acetic acid with sodium hydroxide

Combination Treatment

Calcium and vitamin D will be co-administered to all subjects to prevent a low albumin-adjusted total serum calcium level while taking study drugs. All subjects will receive daily supplementation containing at least 1000 mg of elemental calcium and at least 400 IU vitamin D daily. The dosage of vitamin D will be at least 400 IU daily if screening levels of 25-OH vitamin D is more than 20 ng/mL or at least 800 IU daily if screening levels

of 25-OH vitamin D are 12 to 20 ng/mL. Women with screening levels of 25-OH vitamin D of less than 20 ng/mL will be excluded from the study or can undergo vitamin D repletion. Ergocalciferol is the preferable supplement (for at least 2 weeks), although any other vitamin D supplement can be used according to the local clinical practice.

Sample Size: A sample size of 448 subjects (224 subjects on each MB09 and EU-Prolia [Arm 2 Prolia-MB09 and Arm 3 Prolia-Prolia pooled] at Month 12) will achieve 85% statistical power for the demonstration of equivalence in the %CfB lumbar spine BMD at Month 12, based on the two one-sided 2.5% significance level and an equivalence margin of ±1.45%. In this sample size calculation, the common SD is assumed to be 4.5% and the true mean difference of %CfB is assumed to be zero. Therefore, allowing for a 15% dropout, 528 subjects will be randomised 2:1:1 to the MB09-MB09, Prolia-MB09 and Prolia-Prolia treatment arms.

Populations

Full Analysis Set:

The FAS will consist of all randomised subjects who meet the eligibility criteria and receive at least one dose of study drug.

Modified Full Analysis Set:

The term mFAS will be used to define the analysis data set which includes a data record at each time point for all subjects in the FAS but excludes data observed after the first occurrence of those ICEs where a hypothetical strategy is taken (eg, missing a dose, errors or deviations in dosing, or receipt of any prohibited therapies or other osteoporosis medications). Data in the mFAS will be analysed under the treatment as randomised and used as the primary analysis set for efficacy and PD.

Full Analysis Set for the Transition Period:

The FAS-TP will consist of all randomised subjects in the SAF-TP who progressed to receive a dose of study drug at Month 12, fully meet eligibility criteria and have successfully tolerated the previous two doses of study drug.

Modified Full Analysis Set for the Transition Period:

The term mFAS-TP will be used to define the analysis data set with a data record at each time for subjects in the FAS-TP but excludes data observed after the first occurrence of ICE.

Pharmacokinetic Analysis Sets:

The PK Concentration Sets for the Main Treatment Period (PKCS) and for the Transition Period (PKCS-TP) comprise all subjects who received at least one full dose of study drug (MB09 or EU-Prolia) in the respective period and exclude observations after relevant ICEs which impact PK.

The PK Parameter Set (PKPS) for the Main Treatment Period comprises all subjects who have at least three measurable concentrations in PKCS, which must include Day 11 to allow for reliable estimation of both C_{max} and $AUC_{0\text{-}6\ months}$. The PK Parameter Set for the Transition Period (PKPS-TP) is defined similarly.

Safety Analysis Set:

The SAF will consist of all randomised subjects who received at least one administration of study drug. The SAF will be used for all safety and immunogenicity analyses. In the SAF, subjects will be analysed per the actual treatment received.

Safety Analysis Set for the Transition Period:

The SAF-TP will consist of all subjects in the SAF who progressed to receive a dose of study drug at Month 12, and so thereby enter the Transition Period. The SAF-TP will be used for all safety and immunogenicity analyses of the Transition Period (per the actual treatment received).

Statistical Methods:

Statistical analysis will be performed using SAS® software Version 9.4 or later. Continuous variables will be summarised using the mean, SD, median, minimum value and maximum value. Categorical variables will be summarised using frequency counts and percentages. Data will be listed in data listings. All CIs presented will be 95% (two-sided) CIs. For

primary efficacy, equivalence is demonstrated if the 95% CI falls entirely within predefined margins; this approach is equivalent to two one-sided tests at the 2.5% significance level.

Primary Efficacy Analyses

Primary Efficacy Endpoint - Percentage Change From Baseline in Lumbar Spine Bone Mineral Density to Month 12:

The statistical hypothesis associated with the difference in treatments for the primary efficacy analysis of %CfB in lumbar spine BMD at Month 12 is:

H0: ($\mu_{MB09} - \mu_{Prolia} \leq -1.45\%$) or ($\mu_{MB09} - \mu_{Prolia} \geq +1.45\%$)

H1: $-1.45\% < \mu_{MB09} - \mu_{Prolia} < +1.45\%$

where μ_{MB09} and μ_{Prolia} denote the true mean %CfB in lumbar spine BMD at Month 12 for MB09 and EU-Prolia, respectively.

For the primary efficacy analysis, an MMRM will be fitted to the composite %CfB lumbar spine BMD at Month 6 and Month 12 on the mFAS, including terms for visit by treatment, stratification variables (age, body mass index and prior use of bisphosphonates) included as classification factors and baseline lumbar spine BMD included as a continuous covariate.

The estimated mean difference in %CfB lumbar spine BMD at Month 12 will be presented with 95% CI and equivalence concluded if this falls within predefined equivalence margins of [-1.45%, 1.45%].

Secondary Endpoint Analyses

Secondary efficacy, PD and immunogenicity data will be summarised using appropriate descriptive statistics on the FAS and mFAS for the Main Treatment Period and on the FAS-TP and mFAS-TP for the Transition Period.

Pharmacokinetic concentration and PK data will be listed and summarised using appropriate descriptive statistics on the PKCS and PKPS, respectively, for the Main Treatment Period and on the PKCS-TP and PKPS-TP, respectively, for the Transition Period.

The Main Treatment Period and Transition Period will be analysed separately by treatment or treatment arm on SAF and SAF-TP, respectively.

Version and Date of Protocol: Version 2.0 (Amendment 1), dated 07 November 2022.

List of Abbreviations and Definition of Terms

Abbreviation	Definition
%CfB	percentage change from baseline
25-OH vitamin D	25-hydroxy vitamin D
ANCOVA	analysis of covariance
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
$AUC_{0\text{-}6\ months}$	area under the concentration-time curve from zero to 6 months
AUEC	area under the effect curve
$AUEC_{0\text{-}6\ months}$	area under the effect curve from zero to 6 months
BMD	bone mineral density
CI	confidence interval
C_{max}	observed maximum serum concentration after administration
COVID-19	Coronavirus disease 19
C_{trough}	trough (predose) serum concentration
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EU	European Union
EU-Prolia	EU-Sourced Prolia
FAS	Full Analysis Set
FAS-TP	Full Analysis Set for the Transition Period
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
HIV-1/HIV-2	human immunodeficiency virus subtype-1 and subtype-2
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
INR	International Normalised Ratio
IRT	interactive response technology
L1	first lumbar vertebra
L4	lumbar vertebra 4
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
mFAS-TP	Modified Full Analysis Set for the Transition Period
MI	multiple imputation
MMRM	mixed model for repeated measures
NYHA	New York Heart Association
PD	pharmacodynamic(s)
PFS	pre-filled syringe
PK	pharmacokinetic(s)
PKCS	PK Concentration Set for the Main Treatment Period
PKCS-TP	PK Concentration Set for the Transition Period
PKPS	PK Parameter Set for the Main Treatment Period
PKPS-TP	PK Parameter Set for the Transition Period
PT	prothrombin time
RANK	receptor activator of nuclear factor-ΚΒ
RANKL	receptor activator of nuclear factor-ΚΒ ligand
REC	Research Ethics Committee
RMP	reference medicinal product
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAF	Safety Analysis Set
SAF-TP	Safety Analysis Set for the Transition Period

Abbreviation	Definition
sCTX	serum carboxy-terminal cross-linking telopeptide of type I collagen
SD	standard deviation
SI	International System of Units
SUSAR	suspected unexpected serious adverse reaction
TP	Transition Period
ULN	upper limit of normal
US/USA	United States/United States of America
WHODRUG	World Health Organization Drug Dictionary

Term	Definition
Arm 1 MB09-MB09	Subjects will be administered one subcutaneous injection of MB09 (60 mg/mL) on Day 1, and at Month 6 and Month 12.
Arm 2 Prolia-MB09	Subjects will be administered one subcutaneous injection of EU-Prolia (60 mg/mL) on Day 1 and at Month 6. At Month 12, subjects will be administered one subcutaneous injection of MB09 (60 mg/mL).
Arm 3 Prolia-Prolia	Subjects will be administered one subcutaneous injection of EU-Prolia (60 mg/mL) on Day 1, and at Month 6 and Month 12.
End of Study visit	The End of Study visit will be performed at Month 18 (Transition Period Month 6) for subjects who receive the third dose of study drug at Month 12. Subjects who have the last study drug dose on Day 1 or Month 6 will have their last visit at Month 12.
End of Treatment visit	The End of Treatment visit will be at Month 12 (ie, subjects will receive the third dose of study drug).

1 Introduction

1.1 Background Information

1.1.1 Osteoporosis

Postmenopausal osteoporosis leading to fractures is common and highly costly to health systems. One in every two women will experience an osteoporotic fracture in their lifetime and will be at risk for subsequent fractures. Fractures can cause severe pain and disability (Blackie 2020). The uptake of osteoporosis treatment has declined in recent years and, coupled with fewer than 20% of patients with fractures receiving therapy to reduce the risk of future fractures, drives the need for effective treatment (Kanis et al 2019).

Denosumab has been shown to reduce the incidence of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis (Cummings et al 2009).

1.1.2 Denosumab

Denosumab, the active substance of Prolia®, is a human mAb (IgG2) that targets and binds with high affinity and specificity to the receptor activator of nuclear factor-ΚB ligand (RANKL), preventing activation of its receptor (RANK) on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone (mAbxience 2021).

Prolia was first licensed by the US FDA in June 2010 for the bone loss indications. Prolia was approved by the European Medicines Agency in May 2010 for the treatment of osteoporosis in postmenopausal women at increased risk of fractures and for the treatment of bone loss associated with hormone ablation in men with prostate cancer and in women with breast cancer at increased risk of fractures. In Japan, the product was registered under the brand name Pralia®, which was authorised in March 2013 by the Ministry of Health, Labour and Welfare for the treatment of osteoporosis (mAbxience 2021).

1.2 MB09

MB09 is a medicinal product, containing the mAb denosumab as the active substance, developed by mAbxience as a biosimilar product to the originator RMP Prolia manufactured and marketed by Amgen in Europe and the United States (mAbxience 2021).

1.2.1 Non-clinical Programme

mAbxience has designed an overall development program to establish similarity between MB09 and the RMP according to current regulatory guidelines, tailoring the design of the studies focusing on the mode of action and the analytical similarity between RMP and MB09.

No factors of concern have been identified to date with the similarity data obtained for MB09. This will be further supplemented and confirmed with quality data of additional batches analysed throughout the stepwise approach carried out for the demonstration of biosimilarity. Considering that, the results of in vitro comparative analytical and functional characterisation will continue to be satisfactory and provided there are no findings that preclude the safe use of MB09 in human clinical trials, no in vivo studies will be conducted with MB09 as these are considered more insensitive for the detection of minor differences between biosimilars and the RMP.

1.2.2 Clinical Programme

MB09 is being compared with both EU/US-sourced Xgeva RMPs for safety, PK, PD and immunogenicity in a Phase 1 (Randomized, Double-Blind, Three-Arm, Single-Dose, Parallel Study to compare the Pharmacokinetics, Pharmacodynamics, Safety and Immunogenicity profile of MB09 [proposed denosumab biosimilar] and EU/US-sourced Xgeva® in Healthy Male Volunteers) and with EU-sourced Prolia (EU-Prolia) in the current study.

In the Phase 1 study, it is planned that approximately 255 subjects aged 28 to 55 years will receive in a 1:1:1 ratio a single subcutaneous dose (35 mg) of either MB09 or EU-sourced Xgeva or US-sourced Xgeva). The subjects will be followed for 36 weeks (mAbxience 2021).

1.3 Study Rationale

This multicentre, multinational global comparative efficacy study (MB09-C-01-19) will be conducted as part of a clinical development programme and will assess the therapeutic equivalence in efficacy, safety, PK, PD and immunogenicity of MB09 compared to EU-Prolia. After collecting the totality of evidence proving its biosimilarity to Prolia, MB09 may provide an opportunity to improve access to treatment while delivering substantial cost savings.

The design of this study takes into account the EU Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies: Non-Clinical and Clinical (EMA 2012), PMDA Guideline on the Quality, Safety and Efficacy Assurance of Follow-on Biologics (PFSB/ELD Notification No 0304007 04 March 2009) and the FDA Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (DHHS 2015).

1.3.1 Rationale for Study Population

International regulations (WHO 2009, EMA 2012, DHHS 2015, DHHS 2019) suggest that proposed biosimilars will be tested in a population representative of the approved therapeutic indications of the RMP and sufficiently sensitive for detecting potential differences between the proposed biosimilar and the RMP.

Postmenopausal women with osteoporosis have been selected taking the following into consideration:

- The population is considered sufficiently sensitive to allow the detection of differences between MB09 and Prolia treatment effects, if such a difference exists.
- This population is considered more homogeneous with a well-characterised profile for efficacy and PK due to a reduced disease variability.
- The indication has a well-established effect size.
- This indication is representative, in terms of safety and immunogenicity profile, of the rest of indications as approved for the RMPs.

Postmenopausal female subjects aged ≥55 and ≤80 years, with BMD T-score at the lumbar spine (L1 to L4) or hip ≤ −2.5 SD and ≥ −4.0 SD will be enrolled in this study.

1.4 Risk-Benefit Statement

Detailed information about the known and expected benefits and risks as well as the expected adverse events of MB09 is provided in the Investigator Brochure. A high-level summary of the known benefits and anticipated risks during the study is provided below.

MB09 will have the same pharmaceutical formulation and strength as EU-Prolia (60 mg). The proposed dosing regimen of MB09 in the current study is in line with the approved

EU-Prolia (Prolia SmPC 2020). The proposed safety monitoring is deemed sufficient to monitor the potential risks of MB09 administration. In view of the structural and biological similarity, MB09 is expected to display a safety profile similar to EU-Prolia.

Based upon the proven safety profile of EU-Prolia, the benefits of the proposed current study outweigh the associated risks.

The benefit and risk assessments and the risk mitigation plans for COVID-19 are specified in Appendix 13.3. Risk assessments will be conducted during the study by mAbxience through a detailed discussion with the investigators.

2 Study Objectives, Estimands, and Endpoints

2.1 Primary Objective, Estimands and Endpoint

The primary objective, endpoint and estimands are presented in Table 2-1 and will be studied in the Main Treatment Period.

Table 2-1 Primary Objective and Estimands

Primary Objective	Endpoint and Estimand Descriptions
To demonstrate equivalent efficacy of MB09 to EU-Prolia in postmenopausal women with osteoporosis in terms of lumbar spine BMD at Month 12.	**Endpoint:** Percentage change from baseline (%CfB) in lumbar spine BMD after 52 weeks.
	Estimand 1a (Primary): Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive two denosumab doses without any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications.
	Estimand 1b (Supportive): Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any prohibited therapies or other osteoporosis medications are taken.

[1] Women will not have been previously treated with denosumab but may have had prior treatment with bisphosphonates and will be co-administered calcium and vitamin D supplements.

Abbreviations: %CfB, percentage change from baseline; BMD, bone mineral density; EU-Prolia, EU-sourced Prolia.

Note that Estimands 1a and 1b take primarily hypothetical and treatment policy approaches, respectively, to handle ICEs and a composite strategy for death. The formation of antidrug antibodies and potential adjustments to calcium and vitamin D supplements are not explicitly mentioned in the estimand description summaries above but will be handled by a treatment policy approach in both estimands. Further details of ICEs and more detailed breakdown of the estimand attributes can be found in Section 7.1.

Note: The screening BMD assessment will be taken as the baseline BMD assessment.

2.2 Key Secondary Objectives, Estimands and Endpoints

The key secondary objectives with estimands and endpoints are presented in Table 2-2 for the Main Treatment Period. Other secondary objectives and endpoints are presented in Table 2-3.

Table 2-2 Key Secondary Objectives, Estimands and Endpoints for the Main Treatment Period

Secondary Objectives	Estimand Description (Including *Endpoint*)
To assess the efficacy of MB09 to EU-Prolia in postmenopausal women with osteoporosis in terms of lumbar spine BMD at Month 6, and hip and femur neck BMD at Month 6 and Month 12.	**Estimand 2a\3a\4a:** Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB (zero is taken for anyone who dies) in* • *(2a) lumbar spine BMD after 6 months.* • *(3a) hip BMD after 6 and 12 months.* • *(4a) femur neck BMD after 6 and 12 months.* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive scheduled denosumab dose(s) without any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications. **Estimand 2b\3b\4b:** Same as Estimand 1b for each endpoint above irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any prohibited therapies or other osteoporosis medications are taken.
To assess the PD profile of MB09 to EU-Prolia in postmenopausal women with osteoporosis in terms of sCTX AUEC up to Month 6 and sCTX at Month 12.	**Estimand 5:** Ratio of geometric means (MB09/EU-Prolia) in *sCTX* $AUEC_{0\text{-}6\ months}$ in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming all women receive their first denosumab dose without any errors in dosing and without receipt of any prohibited therapies or other osteoporosis medications up to 6 months after first dose. **Additional summary:** Mean difference in sCTX at 11 days; 1, 3 and 6 months after the first dose; and 6 months after the second dose of study drug.

[1] Women will not have been previously treated with denosumab but may have had prior treatment with bisphosphonates and will be co-administered calcium and vitamin D supplements.

Abbreviations: %CfB, percentage change from baseline; AUEC, area under the effect curve; $AUEC_{0\text{-}6\ months}$, area under the effect curve from zero to 6 months; BMD, bone mineral density; EU-Prolia, EU-sourced Prolia; PD, pharmacodynamic; sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen.

Note: The screening BMD assessment will be taken as the baseline BMD assessment.

Table 2-3 Secondary Objectives and Endpoints for the Main Treatment Period

Secondary Objectives	*Endpoints*
To assess the PK profile of MB09 compared with EU-Prolia.	• *$AUC_{0\text{-}6\ months}$ and C_{max} following the first dose.* • *C_{trough} of serum denosumab at Month 6 and Month 12.*
To evaluate the safety profile of MB09 compared with EU-Prolia.	• *Subject incidence of treatment-emergent adverse events up to and including Month 12.* • *Subject incidence of adverse events of special interest (injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction and atypical femoral fracture) up to and including Month 12.* • *Subject incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG and vital signs from baseline and up to and including Month 12.* • *Subject incidence of deaths and serious adverse events up to Month 12.*
To assess the immunogenicity of MB09 compared with EU-Prolia assessed through antidrug antibodies.	• *Binding and neutralising serum denosumab antibodies from baseline and up to and including Month 12.*

Abbreviations: $AUC_{0\text{-}6\ months}$, area under the concentration-time curve from zero to 6 months; C_{max}, observed maximum serum concentration after administration; C_{trough}, trough (predose) serum concentration; ECG, electrocardiogram; EU-Prolia, EU-sourced Prolia; PK, pharmacokinetic.

The key secondary objectives and endpoints are presented in Table 2-4 for the Transition/Safety Follow-Up Period.

Table 2-4 Key Secondary Objectives, and Endpoints for the Transition/Follow-Up Period

Secondary Objectives	*Endpoints*
To assess the PK profile: i. after the single transition from EU-Prolia to MB09 ii. on MB09 throughout each compared with those on EU-Prolia throughout.	• *Transition Period $AUC_{0\text{-}6\ months}$ and C_{max} following the third dose at Month 12.* • *C_{trough} of serum denosumab at Transition Period Month 6.*
To assess the PD profile: i. after the single transition from EU-Prolia to MB09 ii. on MB09 throughout each compared with those on EU-Prolia throughout.	• *Transition Period sCTX AUEC up to Transition Period Month 6.* • *C_{trough} of sCTX at Month 12 and Transition Period Month 6.*
To assess the risk of hypersensitivity and adverse events: i. after the single transition from EU-Prolia to MB09 ii. on MB09 throughout each compared with those on EU-Prolia throughout.	• *Subject incidence of treatment-emergent adverse events from third dose at Month 12 and up to and including Transition Period Month 6.* • *Subject incidence of adverse events of special interest (injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction and atypical femoral fracture) from third dose at Month 12 and up to and including Transition Period Month 6.* • *Subject incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG and vital signs from third dose at Month 12 and up to and including Transition Period Month 6.* • *Subject incidence of deaths and serious adverse events from third dose at Month 12 and up to and including Transition Period Month 6.*
To assess the risk of immunogenicity through formation of antidrug antibodies: i. after the single transition from EU-Prolia to MB09 ii. on MB09 throughout each compared with those on EU-Prolia throughout.	• *Binding and neutralising serum denosumab antibodies from Month 12 and up to and including Transition Period Month 6.*

Abbreviations: $AUC_{0\text{-}6\ months}$, area under the concentration-time curve from zero to 6 months; AUEC, area under the effect curve; C_{max}, observed maximum serum concentration after administration; C_{trough}, trough (predose)

serum concentration; ECG, electrocardiogram; EU-Prolia, EU-sourced Prolia; PD, pharmacodynamic; PK, pharmacokinetic; sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen.

3 Investigational Plan

3.1 Study Design

This is a randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, PK, PD, safety and immunogenicity of MB09 (proposed denosumab biosimilar) and EU-Prolia in postmenopausal women with osteoporosis.

The study will randomise approximately 528 postmenopausal women with osteoporosis aged ≥55 and ≤80 years old with a BMD consistent with T-score of ≤ -2.5 and ≥ -4 at the lumbar spine or hip as measured by DXA during the Screening Period. Screening evaluations will be completed within 28 days prior to randomisation with the exception of the DXA scan, which would be valid for up to 3 months.

Figure 3-1 shows the study design for the study.

On Day 1, 528 eligible postmenopausal women with osteoporosis will be randomised in a 2:1:1 ratio to receive MB09-MB09 (Arm 1), Prolia-MB09 (Arm 2) or Prolia-Prolia (Arm 3) using an IRT system.

The randomisation will be stratified by baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 SD), body mass index (<25 and ≥25 kg/m^2), age at study entry (≥55 to <68 years versus ≥68 to ≤80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use).

During the Main Treatment Period, subjects will receive one subcutaneous injection (60 mg/mL) of study drug on Day 1 and at Month 6. At Month 12, after all efficacy and safety assessments have been performed, the subject will enter the Transition/Safety Follow-Up Period and will receive the third dose of study drug. Subjects assigned to the MB09-MB09 arm (Arm 1) will receive MB09 on Day 1, at Month 6 and at Month 12. Subjects assigned to the Prolia-MB09 arm (Arm 2) will receive EU-Prolia on Day 1 and at Month 6, and MB09 at Month 12. Subjects assigned to the Prolia-Prolia arm (Arm 3) will receive EU-Prolia on Day 1, at Month 6 and at Month 12. All subjects will be followed up to Transition Period Month 6.

Note: Only subjects who tolerated the initial two doses and are willing to take the third dose should proceed to the Transition/Safety Follow-up Period.

The study visits are as follows (see Figure 3-1 and see Appendix 13.1):

- Visit 1: Screening (-28 days to -1 day)
- Visit 2: Baseline (Day 1) (Main Treatment Period): First administration of study drug
- Visit 3: Day 11 (Main Treatment Period)
- Visit 4: Month 1 (Main Treatment Period)
- Visit 5: Month 3 (Main Treatment Period)
- Visit 6: Month 6 (Main Treatment Period): Second administration of study drug
- Visit 7: Month 9 (Main Treatment Period)
- Visit 8: Month 12 (Main Treatment Period and Transition/Safety Follow-Up Period): Third administration of study drug
- Visit 9: Month 12 + 10 days (Transition Period Day 11)
- Visit 10: Month 12 + 5 weeks (Transition Period Month 1)
- Visit 11: Month 15 (Transition Period Month 3)
- Visit 12: Month 18 (Transition Period Month 6)

The End of Treatment visit will be at Month 12 (ie, subjects will receive the third dose of study drug). The End of Study visit will be performed at Month 18 (Transition Period Month 6) for subjects who receive the third dose of study drug at Month 12. Subjects who have the last study drug dose on Day 1 or Month 6 will have their last visit at Month 12.

Since subjects are required to visit the sites for study drug administration, in the event that subjects cannot visit the study site on the scheduled day for injection, the treatment schedule should be adjusted to remain within the protocol requirements. However, if study drug administration cannot be carried out within an allowed visit window or a missed dose is expected, whether to continue with the subsequent study treatment will be discussed with mAbxience. Ongoing benefit-risk assessment for the clinical study and subject's needs will be assessed.

Appendix 13.3.2 provides details regarding mitigation plans. In the case when site visits are not possible or the subject does not wish to visit the site, remote visits (by means of phone

calls or video calls) or home visits (as a last option) may be allowed for visits that do not include study drug administration or BMD assessments (see Appendix 13.1). Study nurses will be allowed to conduct home visits in order to collect blood samples from the subject. Even if a study visit cannot be made, possible data will be continuously collected via a telephone call and during the next visit, if applicable. The investigator will keep following up with subjects regarding any safety issues (adverse events, concomitant medication) by telephone call before the subjects visit the study site. Note: All remote activities depend on site- and country-specific requirements.

If the subject has known SARS-CoV-2 exposure (even without symptoms related to COVID-19), the study visit for the administration of study drug will be rescheduled at the discretion of the investigator according to local regulations. Treatment with study drug can be re-introduced if the subject has tested negative for COVID-19 or after 2 weeks of symptom-free observation.

Administration of study drug should be interrupted if the subject has documented or presumptive COVID-19 infection until the subject is recovered. Treatment with study drug can be re-introduced in line with local practice following the recovery of the subject and following discussion with the medical monitor and with his/her agreement.

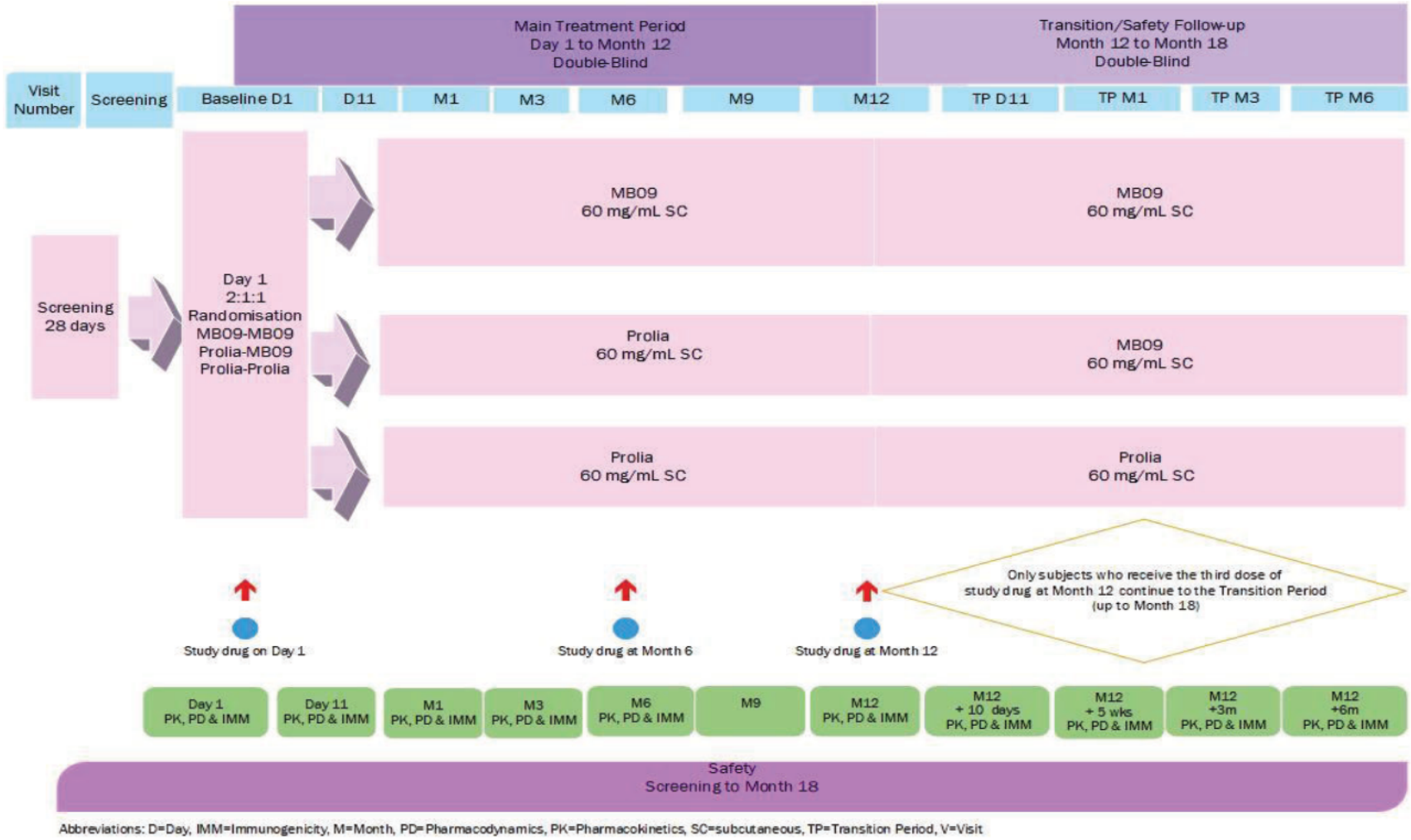
Enrolment of subjects will continue until approximately 528 subjects have been randomised to treatment. The study will be completed when the last subject completes the End of Study visit or withdraws early from the study.

The maximum study duration for a subject will be approximately 19 months: 28 days for screening, a Main Treatment Period of 12 months, and a Transition/Safety Follow-Up Period of 6 months up to Transition Period Month 6.

An independent radiology review committee will assess the BMD (primary efficacy endpoint: %CfB to Month 12 in BMD) using DXA at Month 6 and Month 12.

A DSMB will assess the safety data periodically and will recommend to mAbxience whether to continue, modify, or stop the study. This decision will be based on benefit-risk evaluation (see Section 7.9 for further details).

Figure 3-1 Study Design



Abbreviations: D=Day, IMM=Immunogenicity, M=Month, PD=Pharmacodynamics, PK=Pharmacokinetics, SC=subcutaneous, TP=Transition Period, V=Visit

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Subjects

Approximately 528 subjects will be randomised at approximately 60 sites in Europe and Latin America. In Europe, the study is planned to be conducted in Ukraine, Poland, Czech Republic, Bulgaria, Serbia, Estonia, Georgia and Latvia. In Latin America, the study is planned to be conducted in Mexico. Note: Additional sites or countries may be included in the study.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the eligibility criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Signed informed consent must be obtained prior to participation in the study.
2. Postmenopausal women. Postmenopausal status is defined as at least 12 consecutive months of amenorrhea prior to date of screening with a follicle-stimulating hormone level of ≥30 mIU/mL or surgical menopause (bilateral oophorectomy with or without hysterectomy) ≥12 months prior to the screening visit when follicle-stimulating hormone is not required.
3. Aged ≥55 and ≤80 years at screening (based on age rounded down to the nearest year).
4. Body weight ≥50 kg and ≤99.9 kg, and a body mass index of ≤30 kg/m^2 at screening.
5. Absolute BMD consistent with T-score ≤ -2.5 and ≥ -4 at the lumbar spine or total hip as measured by DXA during the Screening Period.
6. At least two intact, nonfractured vertebrae in the L1 to L4 region (vertebrae to be assessed by central reading of lateral spine X-ray during the Screening Period) and at least one hip joint is evaluable by DXA.

7. Adequate organ function as defined by the following criteria:
    - Normal levels of vitamin D (≥20 to ≤64 ng/mL) and albumin-adjusted total serum calcium (≥8.5 to ≤10.5 mg/dL) at screening.
    - Serum aspartate aminotransferase, alanine aminotransferase and bilirubin ≤2.0 × ULN in the absence of any evidence of viral hepatitis.
    - Platelets ≥100 × 10^9/L.
    - Haemoglobin ≥9.0 g/dL.
    - Albumin 3.4 to 5.4 g/dL.
    - Glomerular filtration rate >30 mL/min.
    - Adequate coagulation parameters such as: INR ≤2.0 and aPTT ≤1.5 × ULN.

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Previous exposure to denosumab (Prolia, Xgeva, or denosumab biosimilar) or any other monoclonal antibody (eg, romosozumab) or fusion protein containing IgG or other biologic agent targeting IgG.
2. Confirmed or suspected with SARS-CoV-2 (COVID-19) at screening or has been diagnosed with COVID-19 or had contact with a COVID-19 infected patient within 14 days of screening. Note: Subjects who have a COVID-19 infection will be allowed to be rescreened if they have a confirmatory negative COVID-19 test result and have completely recovered from COVID-19 before being entered into the study.
3. Height, weight or girth that may preclude accurate DXA measurements.
4. History and/or presence of one severe or more than two moderate vertebral fractures or hip fracture (as determined from the subject's medical history or by the central imaging centre during the Screening Period). Note: All subjects will have an X-ray performed at screening and this radiograph will be used as the reference radiograph that all radiographs performed during the study will be compared to.
5. Recent long bone fracture (within 6 months). Presence of active healing fracture according to assessment of investigators.
6. History and/or presence of bone metastases, bone disease, or metabolic disease other than osteoporosis, which could interfere with the interpretation of the findings, eg, osteogenesis imperfecta, osteopetrosis, osteomalacia, rheumatoid arthritis, Paget's disease, ankylosing spondylitis, Cushing's disease, hyperprolactinemia, malabsorption syndrome, hypoparathyroidism or hyperparathyroidism (irrespective of

current controlled or uncontrolled status), hypocalcaemia or hypercalcaemia (based on albumin-adjusted total serum calcium). Current hyperthyroidism or hypothyroidism are not allowed unless they are well-controlled with stable therapy for at least 3 months prior to baseline and no change of start of therapy for hyperthyroidism or hypothyroidism is anticipated during the study. Subclinical hyperthyroidism (thyroid-stimulating hormone levels <0.1 µU/mL) due to its effect on bone metabolism is not allowed.

7. Malignancy within the 5 years before enrolment (except cervical carcinoma in situ or basal cell carcinoma, which are not prohibitive).
8. Drugs being investigated for osteoporosis.
9. Intravenous bisphosphonate, strontium or fluoride administered for osteoporosis within 5 years of screening.
10. Oral bisphosphonates ≥12 months cumulative use prior to screening. If used <12 months cumulatively and the last dose was ≥12 months before screening, the subject can be enrolled.
11. Ongoing use of any osteoporosis treatment (excluding calcium and vitamin D supplements) taken within the past 5 years prior to screening, with the exception of the medications listed below that are required to adhere to rules for the following washout periods:
    - Tibolone, oestrogen/progesterone containing products including any oestrogen/progesterone contraceptives or hormone-replacement therapy, selective oestrogen receptor modulators, received within 3 months prior to screening.
    - Calcitonin, calcitriol, maxacalcitol, falecalcitriol or alfacalcidol: dose received within 3 months prior to screening.
    - Cinacalcet: dose received within 3 months prior to screening.
    - Parathyroid hormone or parathyroid hormone derivatives within the last 3 months before initial administration of the study drug.
12. Other bone active drugs including heparin, warfarin, antiplatelet therapy (clopidogrel), anticonvulsives (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin-releasing hormone agonists, anabolic steroids, aluminium, aromatase inhibitors, protease inhibitors, methotrexate and thiazolidinediones within the past 3 months before initial administration of the study drug. Note: Direct oral anticoagulants are allowed as they have no effect on bone metabolism.

13. Systemic glucocorticosteroids (≥5 mg prednisone equivalent per day for ≥10 days or a total cumulative dose of ≥50 mg) within the past 3 months before screening.
14. Use of certain immunosuppressants (eg, calmodulin and calcineurin inhibitors) within the past 3 months prior to screening.
15. Chronic treatment of protein pump inhibitors if used continuously for longer than a year within the past 3 months prior to screening.
16. Use of other investigational drugs within five half-lives of the drug or until the expected pharmacodynamic effect of the drug has returned to baseline or within 30 days prior to screening, whichever is longer, or longer if required by local regulations.
17. Oral or dental conditions: osteomyelitis or history and/or presence of osteonecrosis of the jaw, presence of risk factors for osteonecrosis of the jaw (eg, periodontal disease, poorly fitting dentures, invasive dental procedures such as tooth extractions in 6 months before screening), active dental or jaw condition which requires oral surgery and/or planned invasive dental procedure at the discretion of the investigator. Note: Subjects may be further examined by a dental specialist at the investigator's discretion.
18. Vitamin D deficiency (25-OH vitamin D serum level <20 ng/mL). Vitamin D repletion is permitted at the investigator's discretion and subjects will be rescreened to re-evaluate vitamin D level post repletion. Vitamin D levels will be re-tested once within the Screening Period.
19. Known intolerance to, or malabsorption of calcium or vitamin D supplements.
20. History and/or presence of a severe allergic reaction (eg, general anaphylaxis).
21. Has an active infection that required the use of oral antibiotics within 2 weeks or parenteral antibiotics used within 4 weeks prior to randomisation. Has an HBV, HCV, HIV-1/HIV-2 or SARS-CoV-2 positive test result at screening. If a positive test result is obtained, a confirmatory test is required.
22. Received a COVID-19 vaccine within 14 days prior to randomisation to study drug or is planning to receive a COVID-19 vaccine within 14 days prior to study drug administration at Month 6 or Month 12.
23. History and/or presence of significant cardiac disease as per investigator's discretion, including but not restricted to: ECG abnormalities at screening indicating significant risk of safety for subjects participating in the study, history and/or presence of myocardial infarction within 6 months before screening, history and/or presence of NYHA class III or IV heart failure, any unstable pulmonary disease (eg, chronic

obstructive disease), hematologic, neurological, psychiatric, endocrine (eg, diabetes), autoimmune disease (eg, Crohn's disease or coeliac disease), gastrointestinal, renal, urinary, skeletal or dermatologic disease, which can be judged as clinically significant at the investigator's discretion.

24. Subject has a history or current evidence of any condition, therapy, laboratory abnormality or other circumstances that might, in the opinion of the investigator, confound the results of the study, interfere with the subject's ability to comply with the study procedure, or make participation in the study not in the subject's best interest.
25. Currently abuses alcohol or drugs or has a history of alcohol or drug abuse within 12 months prior to the first administration of the study drug.
26. Have major surgery (including surgery to bone), or significant traumatic injury occurring within 4 weeks before randomisation or if one is planned during the study.
27. Have immobility due to severe or chronically disabling conditions.

4.1.3 Subject Enrolment and Registration

To differentiate between screened and randomised subjects, within the Electronic Data Capture System/IRT, the following process must be adhered to:

- Each subject should have a unique subject screening number.
- Once the subject's eligibility has been successfully confirmed, the subject will be randomised and assigned a unique randomisation number.
- If the subject withdraws study participation before/after the baseline visit (Visit 2), her screening number cannot be used for another subject.
- Investigator(s) should keep a record (the subject screening log) of subjects who entered screening.

The investigator(s) will:

- Obtain signed informed consent from the potential subject before any study-related procedures are performed.
- Determine subject eligibility.

4.1.4 Screen Failures

Subjects who have a COVID-19 infection at screening will be allowed to be rescreened on the basis that they have a confirmatory negative COVID-19 test result and have completely recovered from COVID-19 before being entered into the study. Rescreening for subjects with confirmed COVID-19 is further discussed in Appendix 13.3.

Where a subject does not meet all the eligibility criteria but is incorrectly started on study drug, the investigator should inform the medical monitor. The subject should remain in the study for 6 months of safety follow-up only. The medical monitor must ensure all decisions are appropriately documented.

Subjects who fail screening for technical reasons can be rescreened only once. If there is an unusual situation so that additional rescreening will be considered, the investigator is recommended to discuss with mAbxience. A rescreened subject will be assigned a new subject identification number.

The reason for screen failure will be collected in the clinical database. The following information, at a minimum, will be collected in the source documents for subjects who failed screening: reason for screen failure, informed consent, age, race, ethnicity, adverse events from the date of informed consent until the subject is considered to have failed screening by the investigator, and the investigator's signature. Inclusion/exclusion criteria for screen failures will be documented in the source documents and in the eCRF.

4.2 Managing Subject Events on the Study

4.2.1 Discontinuation From Study Drug

A subject should permanently discontinue (definitive discontinuation) the study drug if:

- The subject was dosed in error because they did not meet the eligibility criteria of the study; exceptionally, subjects with osteoporosis, with no safety concerns and with potential clinical benefit may continue in the study as per PI discretion.
- The subject experienced tolerability issues (serious or intolerable adverse events, laboratory safety results of concern).
- The subject developed contraindications of use of study drug.

In the case of an ineligible and discontinued subject, a safety follow-up up to 6 months (after the last dose of study drug) is required only. In the case of tolerability or contraindication issues being the reason for treatment discontinuation, the subject should be asked to complete the schedule of visits to the end of the Main Treatment Period at Month 12.

If the subject has concerns about the burden or inconvenience of study procedures, then they should be asked if they would return just for the Month 12 visit as this is a critical visit for safety follow-up and the primary endpoint for the study to meet its primary objective. **Data at Month 12 are important and should be collected even if the subject transitioned to different osteoporosis medications (including those prohibited in the study) or missed the second dose of study drug or intermediate visits.**

The reason for discontinuing study drug should be collected and categorised as related or not related as follows:

- **Related to** dissatisfaction with the study drug (eg, lack of efficacy, intolerability, side effects, discomfort or preference for another product).
- **Not related to** dissatisfaction with the study drug.

4.2.2 Adjustments to Calcium and Vitamin D Supplements

Adjustments (including interruption or discontinuation) to calcium and vitamin D supplements can be made in managing hypercalcaemia, hypocalcaemia or intolerance (see Section 5.2.2.1). Subjects can remain in the study and on study drug throughout.

4.2.3 New Fractures

The investigator should ensure that new fractures are to be reported as adverse events. The investigator should not consider new fractures as a reason for study discontinuation. New fractures will be treated per standard of care and at the discretion of the investigator.

Any adverse event(s) will be continued to be followed until resolution and documented in the eCRF according to Section 6.5.1.4.

4.2.4 Discontinuation Prior to the Transition Period

Subjects who wish to discontinue the study treatment prior to receiving the third dose of study drug at Month 12 should be transitioned to other osteoporosis medications at the

investigator's discretion as per their standard of care and discontinued from the study at Month 12 after the Month 12 assessments have been performed.

4.2.5 Medical Care of Subjects After Discontinuing Study Drug

After the subject has discontinued study drug, medical care provided to the subject will be at the discretion of the investigator following institutional standard of care.

Data at Month 12 are important and should be collected even if the subject has transitioned to different osteoporosis medications. Note: BMD, osteoporosis medication and safety data will be recorded in the eCRF as described in Section 6.1.1, Section 5.8 and Section 6.5, respectively.

4.2.6 Lost to Follow-Up

A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, two telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

If the subject continues to be unreachable, they will be considered to have withdrawn from the study. **If the subject can be reached, the subject should be encouraged to return for at least the Month 12 visit if possible, for safety follow-up.** If the subject wishes to withdraw from the study, then the reason should be recorded.

4.3 Withdrawal From the Study

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. The investigator should discontinue a subject from the study, if they think that continuation would be detrimental to the subject's well-being.

Subjects who wish to discontinue from the study drug should be encouraged to partially remain in the study if possible, and attend the Month 12 visit, regardless of whether they have received the second dose of study drug, with the aim to collect as much efficacy and safety data as possible (particularly at Month 12, as it is critical for the primary endpoint).

The reason(s) for withdrawing from the study will be recorded.

If necessary, the investigator should discuss any subject's reason for withdrawal from the study with mAbxience, or its designee.

4.3.1 Partial Withdrawal From the Study

Subjects are encouraged to attend the Month 6 and Month 12 visits, and there are two levels of withdrawal defined:

- Complete withdrawal from any point in the study.
- Partial withdrawal (subjects returning for Month 6 and/or Month 12 only, where they may receive a dose of study drug at Month 6 and will not be dosed at Month 12).

4.3.2 Reasons for the Investigator to Withdraw the Subject

Follow-up of all dosed subjects for safety evaluation to 6 months after the last dose is preferred if possible. A subject who does not meet the protocol-defined eligibility criteria should not proceed in the study except for the 6-month safety follow-up (with the exception of subjects with osteoporosis and dosed in error because they did not meet the eligibility criteria of the study but without safety concerns and with potential clinical benefit in the opinion of the PI, as those may continue in the study as per investigator discretion).

At the discretion of the investigator, the following reasons may warrant partial or complete withdrawal of a subject from the study:

1. Serious or intolerable adverse event.
2. New symptoms or an intercurrent illness not consistent with the protocol requirements.
3. New contraindications of use of study drug.
4. Death.

4.3.3 Sponsor Termination of the Study

The sponsor (mAbxience) reserves the right to terminate the study at any time for reasonable medical and/or administrative reasons. This termination will occur after consultation with the investigator, if possible. If the study is terminated prematurely by mAbxience, all subjects will be notified regarding the next steps in their study participation, and an appropriate follow-up examination of the subject will be arranged. The investigator will inform the IEC/REC of any premature termination or suspension of the study, where applicable.

4.3.4 Subject Decision to Withdrawal From the Study

Although a subject is not obliged to give their reason(s) for permanent withdrawal from the study, the investigator should make every effort to ascertain the reason(s) while fully respecting the subject's rights. If there is a medical reason for withdrawal, the subject will remain under the supervision of the investigator until satisfactory health has returned or the subject's status is stabilised.

The subject will be asked to indicate whether their reason for withdrawal from the study is due to:

- Burden of study procedures.
- Unrelated medical conditions.
- Any other reason.

If the reason of study withdrawal is due to the burden of the study, the subject will be asked if they would return for the Month 6 and Month 12 visits only and may choose to receive the second dose of study drug at Month 6. Thus, they will have the option of complete (see Section 4.3) or partial (see Section 4.3.1) withdrawal.

4.3.5 Replacements

Subjects who receive study drug and discontinue the study before the study completion will not be replaced.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Arms

Subjects will be randomly assigned at the baseline/randomisation visit (Visit 2) to receive in a 2:1:1 ratio to receive MB09-MB09 (Arm 1), Prolia-MB09 (Arm 2) or Prolia-Prolia (Arm 3).

Interactive response technology will be used to administer the randomisation schedule. Biostatistics will generate the randomisation schedule using SAS® software Version 9.4 or later (SAS Institute Inc., Cary, North Carolina) for IRT, which will link sequential subject randomisation numbers to treatment codes. The randomisation schedule will be stratified by baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 SD), body mass index (<25 and ≥25 kg/m^2), age at study entry (≥55 to <68 years versus ≥68 to ≤80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use).

5.2 Treatments Administered

5.2.1 MB09 and EU-Sourced Prolia

MB09 (60 mg) or EU-Prolia (60 mg) will be administered using a PFS of 60 mg/mL solution on Day 1, and at Month 6 and Month 12. The study drug will be administered as a subcutaneous injection in the upper arm, upper thigh or abdomen. See Section 6.5.6.2 and Section 6.5.6.3 respectively, for injection site reaction and hypersensitivity/allergic reaction monitoring details.

The study drug is required to be administered by the study site-qualified and trained clinical staff member(s) (eg, nurse/physician, etc), designated as an unblinded study site personnel who will not be involved in any other study-related procedure(s). Subjects will be blinded through the use of a blindfold, screen or similar method during the dosing procedure so that the injection syringe will not be visible to the subject. The details regarding blinding are described in Section 5.6.

MB09 and EU-Prolia should be visually inspected prior to its use. The study drug solution should not be injected if it is cloudy or discoloured or if it contains many particles or foreign particulate matter. To avoid discomfort at the site of injection, the PFS should be allowed to

reach room temperature (up to 25ºC) before injecting and inject slowly. The entire contents of the PFS should be injected.

5.2.2 Co-Administration of Calcium and Vitamin D

Calcium and vitamin D will be co-administered to all subjects to prevent a low albumin-adjusted total serum calcium level while taking study drugs. All subjects will receive daily supplementation containing at least 1000 mg of elemental calcium and at least 400 IU vitamin D daily. The dosage of vitamin D will be at least 400 IU daily if screening levels of 25-OH vitamin D are more than 20 ng/mL or at least 800 IU daily if screening levels of 25-OH vitamin D are 12 to 20 ng/mL. Women with screening levels of 25-OH vitamin D of less than 20 ng/mL will be excluded from the study or can undergo vitamin D repletion. Ergocalciferol is the preferable supplement (for at least 2 weeks), although any other vitamin D supplement can be used according to the local clinical practice. See Section 5.4.3 for information regarding calcium and vitamin D provision.

Subjects will receive daily calcium and vitamin D from randomisation until the End of Study visit (Transition Period Month 6). Information about calcium and vitamin D administration will be recorded in both the source documents and eCRF.

5.2.2.1 Managing Hypercalcaemia and Hypocalcaemia

If a subject develops hypercalcaemia during the study, the calcium and/or vitamin D supplementation may be interrupted or reduced per the investigator's discretion until the albumin-adjusted total serum calcium concentration has returned to the normal range.

It is important to identify subjects at risk for hypocalcaemia (Prolia USPI 2020, Prolia SmPC 2020). Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy with study drug. Per Prolia USPI 2020 and Prolia SmPC 2020, clinical monitoring of albumin-adjusted total serum calcium levels is recommended before each dose of study drug and in subjects predisposed to hypocalcaemia within two weeks after the initial dose of study drug. If any subject presents with suspected symptoms of hypocalcaemia during study drug treatment, albumin-adjusted total serum calcium levels should be measured during an unscheduled visit. After each administration of study drug at Day 1 and Month 12, albumin-adjusted total serum calcium levels will be

monitored as part of the clinical chemistry panel on Day 11 and Transition Period Day 11, respectively. Subjects should be encouraged to report symptoms indicative of hypocalcaemia.

If a subject develops hypocalcaemia, defined as albumin-adjusted total serum calcium <8.5 mg/dL (<2.125 mmol/L) during the study, appropriate additional supplementation will be instituted as deemed acceptable by local guidelines to return the albumin-adjusted total serum calcium concentration to within the normal range.

If a subject is intolerant of the daily calcium or vitamin D supplementation, the formulation may be changed (including taking a preferred product that the subject tolerated well earlier) or the dose can be lowered per the investigator's discretion. The intolerance as well as the resolution (eg, change in formulation or dosage) will be recorded in both the source documents and the eCRF.

5.3 Identity of Study Drug

MB09 is a medicinal product, containing the mAb denosumab as the active substance, developed by mAbxience as a biosimilar product to the originator RMP Prolia. Denosumab, the active substance of MB09, is a full-length human mAb of the IgG_2 subtype produced in a mammalian cell line, Chinese hamster ovary cells, by recombinant DNA technology. Denosumab consists of two heavy chains and two light chains of the kappa subclass, with an approximate molecular weight of 147 KDa. The International Nonproprietary Name of the commercially available reference material (Prolia) is denosumab and the ATC Classification System code is M05BX04.

The RMP, EU-Prolia, is supplied as sterile, preservative-free, clear, colourless to slightly yellow solution for subcutaneous administration. Each 1 mL single-dose PFS of Prolia contains 60 mg denosumab (60 mg/mL solution), 4.7% sorbitol (E420), glacial acetic acid, sodium hydroxide, polysorbate 20, and water for injection (Prolia SmPC 2020).

MB09 is supplied as a sterile, preservative-free, colourless to slightly yellow solution. Each 1 mL single-dose PFS of MB09 contains 60 mg denosumab (60 mg/mL), 4.6% sorbitol, 18 mM acetic acid, 0.01% polysorbate 20, water for injection, and sodium hydroxide to a pH of 5.2. The PFS comprises a clear type I borosilicate glass PFS with a 29-gauge thin-walled stainless steel needle, rigid needle shield, and a plunger rod. For further details, see mAbxience 2021.

The following drug supplies will be used in the study:

Product	Supplied As:
MB09	60 mg/mL single-dose PFS
EU-Prolia	60 mg/mL single-dose PFS

Abbreviations: EU-Prolia, EU-sourced Prolia; PFS, pre-filled syringe.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

Study drug will be manufactured per GMP Annex 13. The study drug subject kit will be allocated to each subject via the IRT system at the baseline/randomisation visit (Visit 2). A label will be attached to the outside of each subject kit, as well as to the immediate container. The text will be compliant with local regulatory requirements and may include some of the following information:

- Protocol number.
- Subject number/study site number.
- Contents and quantity.
- Kit number.
- Randomisation code/kit number.
- Investigator's name.
- Route of administration.
- Directions for use.
- Storage instructions.
- Caution statement (for clinical study use only).
- Sponsor's contact name and address.
- Expiry date.

Storage and handling requirements are identical to that for EU-Prolia and will be followed when handling MB09. All study drug supplies must be stored in a secured area with limited

access (eg, a locked cabinet) and in accordance with the manufacturer's instructions. They will be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and will not be frozen. The immediate containers must be kept in the outer carton until use to protect the study drug from light and heat and avoid vigorous shaking. Once removed from the refrigerator, the product must not be exposed to temperatures above 25°C or direct light and must be used within 14 days. The recommended storage conditions and expiry date, where required, are stated in the product label approved by each regulatory authority. Once removed from the refrigerator, the study drug kits will be used on the same day. If not used for any reason, the kit will be discarded.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received, and any discrepancies are reported and resolved before use of the study drug.

5.4.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Only subjects enrolled in the study may receive the study drug and only authorised site personnel may supply or administer the study drug. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

The investigator agrees not to supply the study drug to any person other than subinvestigators, designated staff, and the subjects participating in the study. Study drug may not be relabelled or reassigned for use by other subjects unless approved by mAbxience. The investigator agrees to neither dispense the study drug from, nor store it at, any study site other than the study sites agreed upon with mAbxience.

The used syringes can only be destroyed if it is according to local standard operating procedures and a specific authorisation is given by mAbxience. Permission will be granted by mAbxience on a study-site-by-study-site basis after reviewing the study site destruction

policy. This authorisation may also be granted to destroy used syringes immediately after administering the study drug to subjects in a manner that preserves the blinding. The list of destroyed syringes must be recorded.

5.4.3 Other Supplies

Calcium and vitamin D will be supplied locally to the subject by the site per local regulations to ensure that all subjects will receive a formulation of calcium that contains at least 1000 mg of elemental calcium (see Section 5.2.2 for further information regarding doses).

5.5 Medication Errors

The study drug is a single-use formulation that will be administered at the site by the unblinded designated personnel on Day 1, Month 6 and Month 12. It is highly unlikely that there will be a medication error. Any medication errors will be recorded in both the source documentation and eCRF.

5.6 Blinding

This study will remain double-blinded until the end of all follow-up procedures. The randomisation codes will not be revealed to study subjects, investigators, or study site personnel, except for delegated unblinded staff who will handle the study drug, and predefined unblinded mAbxience and PPD personnel, until all final clinical data have been entered into the database and the database is locked and released for analysis.

The trained clinical staff member(s) responsible for drug administration (eg, nurse/physician, etc) will be designated as unblinded study site personnel and will not be involved in any clinical or safety evaluations that are part of the blinded protocol or have other subject contact. Subjects will be blinded through the use of a blindfold, screen, or similar method during the dosing procedure so that the injection syringe will not be visible to the subject. Blinded staff will be absent during study drug administration and will remain blinded throughout the study.

Unblinded staff will be required to visually inspect the study drug prior to its use. The solution may contain trace amounts of translucent to white proteinaceous particles. The study drug is not to be injected if it is cloudy or discoloured or if it contains many particles or foreign particulate matter (refer to mAbxience 2021 for further details).

5.6.1 Breaking the Blind

Under normal circumstances, the blind will not be broken. The blind will be broken only if specific emergency treatment that will be dictated by knowing the study drug assignment is required for medical management. In such cases, the investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure in the IRT (see IRT manual, which is provided as a separate document). In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual subject's treatment allocation.

The date, time, and reason for the unblinding must be documented in the appropriate field of the eCRF, and the medical monitor must be informed as soon as possible. All calls resulting in an unblinding event will be recorded and reported by the IRT to the medial monitor and mAbxience. Any subject for whom the blind is broken may continue in the study and receive study drug (per protocol) at the investigator's discretion.

mAbxience's Pharmacovigilance Department will have access to the randomisation code, if SUSARs, which are subject to expedited reporting, will be unblinded before submission to the regulatory authorities.

The overall randomisation code will be broken only for reporting purposes. This will occur after database lock for data up to the end of Month 12 for all subjects. The unblinded personnel will be predefined and documented before breaking the study blind. The study will remain blinded to the investigators, subjects, and predefined mAbxience and PPD blinded personnel until all subjects have completed the study and the database has been finalised for study closure.

To the extent possible before unblinding, the investigator will contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that subject. The treatment assignment will be unblinded through IRT. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

5.7 Compliance With Study Treatment

MB09 and EU-Prolia will be administered by delegated unblinded study staff while the subject is at the study site (see Section 5.6 for further blinding details). The date and time of

each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study drug and study subject identification will be confirmed at the time of dosing by a member of the study site personnel other than the person administering the study drug.

Every effort will be made to encourage the subjects' compliance with the study visits. If any study visit has to be rescheduled, subsequent visits will follow the original visit date scheduled. A dosing visit window of ±10 days is allowed for Visit 6 (Month 6) and Visit 8 (Month 12) (Appendix 13.1).

5.8 Prior, Concomitant, Medications and Therapies

Information (eg, drug name, date[s] of administration, etc) about prior medications taken by the subject within 30 days prior to the signed date of ICF (inclusive of the applicable periods for prohibited medications as defined in Section 5.9) will be recorded until the End of Study visit in both the source documents and eCRF. In order to check eligibility, medication history will be reviewed for the exclusion criteria (exclusion criterion #1, exclusion criterion #8, exclusion criterion #9, exclusion criterion #10, exclusion criterion #11, exclusion criterion #12, exclusion criterion #13, exclusion criterion #14, exclusion criterion #15, exclusion criterion #16 and exclusion criterion #22). This will include all prescription drugs, over-the-counter medicines, vitamins and herbal supplements.

All concomitant medications should remain stable during the study and any new concomitant medications that could possibly affect the efficacy results should be consulted with the medical monitor. Subjects should be encouraged to remain on their baseline concomitant medications and advise the investigator when their primary care physician performs any changes to their usual therapy.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. All concomitant medications will be reported to the investigator and recorded on the appropriate eCRF page and source document. Any changes in concomitant medications also will be recorded in the source documents and eCRF. All concomitant medications used until the End of Study visit will be recorded.

Use of all prior and concomitant medications for the treatment of osteoporosis, from the diagnosis of the disease until the End of Study visit, will be recorded in the subject's source

documents and eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded.

Any COVID-19 vaccination must be recorded on the concomitant page of the eCRF including all available data (tradename, manufacturer, Marketing Authorisation Holder, data and time of vaccination and batch number whenever available).

It is the investigator's responsibility to ensure that details regarding the medication are adequately recorded in both the source documents and eCRF.

5.9 Prohibited Concomitant Therapy

The following medications, treatments or procedures are prohibited during the study. Subjects who have received or plan to receive these prohibited medications or treatments will not be enrolled in the study (Section 4.1.2). Subjects who receive any prohibited therapy during the Screening Period will be considered a screen failure. Intake of prohibited therapy by the subjects after randomisation will be considered as a protocol deviation (Section 11.2.2). If a subject takes a prohibited medication, they will remain in the study in order to collect safety follow-up information as well as the efficacy assessments at Month 6 and Month 12. These subjects will be treated with standard of care per local guidelines by the investigator. Note: Bone active drugs as per standard of care are allowed to be administered to the subject. Subjects who withdraw from the study and receive other osteoporosis medications will be encouraged to attend Month 6 and Month 12 visits for the BMD and safety follow-up.

Medication may be administered for the treatment of adverse events or emergency treatment at any time during the study and must be recorded in the eCRF.

Table 5-1 presents a summary of prohibited medications with washout periods.

Table 5-1 Summary of Prohibited Medications With Washout Periods

Prohibited Medications	Washout Period(s)
1. Denosumab (Prolia, Xgeva or biosimilar denosumab) other than study drugs or any other monoclonal antibodies (eg, romosozumab), protein, fusion protein or other biologic agent targeting IgG.	Never.
2. Drugs being investigated for osteoporosis.	Never.
3. Intravenous bisphosphate, strontium or fluoride administered for osteoporosis.	Within 5 years of screening.
4. Oral bisphosphonates.	Not allowed if used ≥12 months cumulatively prior to screening. Allowed, if used for <12 months cumulatively and the last dose was ≥12 months before screening.
5. Any osteoporosis treatment (excluding calcium and vitamin D)**, with the exception of the medications listed below that are required to adhere to rules for the following washout periods**:	5 years prior to screening
• Tibolone, oestrogen/progesterone containing products including any oestrogen/progesterone contraceptives or hormone-replacement therapy, selective oestrogen receptor modulators.	3 months prior to screening.
• Parathyroid hormone or parathyroid hormone derivatives.	3 months prior to initial administration of study drug.
• Calcitonin, calcitriol, maxacalcitol, falecalcitriol or alfacalcidol.	3 months prior to screening.
• Cinacalcet.	3 months prior to screening.
6. Other bone active drugs including heparin, warfarin, antiplatelet therapy (clopidogrel), anticonvulsives (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin-releasing hormone agonists, anabolic steroids, aluminium, aromatase inhibitors, protease inhibitors, methotrexate and thiazolidinediones. Note: Direct oral anticoagulants are allowed as they have no effect on bone metabolism.	3 months prior to initial administration of study drug.
7. Systemic glucocorticosteroids (≥5 mg prednisone equivalent per day for ≥10 days or a total cumulative dose of ≥50 mg).	3 months prior to screening.
8. Use of certain immunosuppressants (eg, calmodulin and calcineurin inhibitors).	3 months prior to screening.
9. Chronic treatment of protein pump inhibitors if used continuously for longer than a year.	3 months prior to screening.

Prohibited Medications	Washout Period(s)
10. Other investigational drugs.	Within five half-lives of the drug or until the expected pharmacodynamic effect of the drug has returned to baseline or within 30 days prior to screening, whichever is longer, or longer if required by local regulations.
11. COVID-19 vaccine.	Within 14 days prior to randomisation to study drug administration, or within 14 days prior to study drug administration at Month 6 or Month 12.

Abbreviations: COVID-19, coronavirus disease 19; IgG, immunoglobulin G.

Subjects who complete the study or are permanently discontinued from the study drug can be transitioned to any osteoporosis medication at the investigator's discretion.

5.10 Intervention After the End of the Study

MB09 will not be available to subjects after the end of the study.

6 Study Assessments and Procedures

Before any study procedures are performed, all potential subjects will sign an ICF. Subjects will have the opportunity to have any questions answered prior to signing the ICF. The investigator must address all questions raised by the subject. The investigator or designee will also sign the ICF and a copy of the signed and dated ICF will be provided to the subject. Additional procedural details related to the ICF are provided in Section 9.3.

All subjects will return to the study site at regular scheduled time intervals for clinical assessments and blood samplings. The total volume of blood collected for each assessment is discussed in the laboratory manual. Subjects will undergo the procedures at the time points specified in the Schedule of Events (Appendix 13.1). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

6.1 Efficacy Assessments

6.1.1 Bone Mineral Density

Bone mineral density will be assessed by DXA scan at the time points specified in the Schedule of Events (Appendix 13.1) using validated instruments. All DXA scans will be analysed by the central imaging vendor. The same DXA instrument will be used for all study procedures for each subject during the study. If, for unforeseeable reasons, the same scanner is no longer available, the study site will follow the central imaging provider's guidance on selecting an appropriate replacement scanner and follow a phantom scanning process to quantify any calibration differences. This will be documented in the Imaging Manual. Assessment of the lumbar spine, total hip, and femoral neck BMD will be performed by an independent blinded central reader at each specified time point. Quality control measures will be in place to maintain accuracy and precision of BMD measurements. All DXA scan images will be read centrally, and efficacy analyses will be based on centrally read results.

Primary efficacy assessment will be determined by percentage change in BMD at the lumbar spine from baseline to Month 12. Secondary efficacy assessments include percentage change in BMD at the lumbar spine from baseline to Month 6 and percentage change in BMD in total hip and femoral neck BMD at Month 6 and Month 12.

For lumbar spine DXA scan, L1 to L4 will be measured, only excluding vertebrae that are affected by local structural change or artefact, using at least two vertebrae for diagnostic

classification. Anatomically abnormal vertebrae may be excluded from analysis if they are clearly abnormal and nonassessable within the resolution of the system and using a 1.0 T-score difference between vertebra in question and adjacent vertebrae as a guideline in identifying vertebrae for exclusion (ISCD 2019).

For femur DXA scan, the left side will be used for all scans at all study visits. If the right side must be used (eg, due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study. If a subject fractures the hip that has been scanned during the study up to the time of fracture, no further scans will be obtained for the affected location.

6.1.2 Screening Bone Mineral Density Assessment

To determine eligibility based on BMD T-score, lumbar spine DXA scans will be analysed by the central imaging vendor.

For screening purposes, DXA scans of the lumbar spine taken up to 3 months for the screening evaluation may be used if all of the following criteria are met:

- Images were obtained by a trained technician.
- DXA images were obtained using the same DXA instrument that will be used for this study.

To be eligible for the study, subjects must have at least two evaluable vertebrae at the lumbar spine (L1 to L4) and at least one evaluable hip by DXA scan assessed by the central imaging vendor. Subjects with unilateral hip prostheses will be allowed to enrol and the contralateral hip will be used for evaluation.

6.1.3 On-Study Bone Mineral Density Assessment

Bone mineral density changes for individual subjects will be monitored by the central imaging vendor during the study per the time points specified in the Schedule of Events (Appendix 13.1). Investigators will be alerted by the central imaging vendor if a subject experiences a BMD loss from baseline of 7% or more at the lumbar spine or total hip, or if the BMD T-score drops below –4.0 at lumbar spine or total hip during the study.

6.1.4 Radiography

Lateral spine radiographs will be performed at screening only. Additional radiographs will be performed as required during the study for confirmation of suspected new clinical fractures. Radiographs will be assessed by quantitative grading at a central imaging centre. Any new fractures confirmed by the central imaging vendor will be recorded as an adverse event.

New clinical fractures include vertebral fracture, non-vertebral fracture and hip fracture that are associated with signs and symptoms indicative of a fracture.

A new vertebral fracture is defined as an increase of at least one grade in any vertebra from T4 to L4 that was normal at screening (Cummings et al 2009). The lateral spine X-ray for vertebral fracture as well as copies of other diagnostic image and/or radiology report, surgical report, or discharge summary will be included in the subject's individual source documents and will be submitted to the central imaging vendor for confirmation of fracture. The central imaging vendor will inform the study sites if a vertebral fracture is identified. The new vertebral fracture will be assessed by semi-quantitative grading at a central imaging vendor (Genant et al 1993):

- Grade 0 = no fracture.
- Grade 1 = mild fracture, 20% to 25% reduction in vertebral height (anterior, middle, or posterior).
- Grade 2 = moderate fracture, greater than 25% to 40% reduction in any height.
- Grade 3 = severe fracture, greater than 40% reduction in any height.

Information about new non-vertebral fracture (eg, details regarding the type of fracture and other pertinent data) and level of trauma causing the fracture will be recorded during the study. A copy of other diagnostic image and/or radiology report, surgical report, or discharge summary will be included in the subject's individual source documents and will be submitted to the central imaging vendor for confirmation of fracture. If the radiograph or diagnostic image is not available, then, at minimum, a copy of the radiology report, surgical report, clinical notes, or discharge summary will be submitted to the central imaging vendor.

If necessary to support the subject's medical care, these X-rays could be read locally.

6.2 Pharmacokinetics

Pharmacokinetic blood samples for the determination of serum concentrations of denosumab will be collected from subjects in the Main Treatment Period and Transition/Safety Follow-Up Period at the time points specified in the Schedule of Events (Appendix 13.1). The total volume of blood collected for PK assessments is discussed in the laboratory manual. The sample collection tube may be changed during the study and details will be provided in the laboratory manual.

Analysis will be performed at the central laboratory using validated bioanalytical methods.

Predose samples (Day 1, Month 6 and Month 12) will be collected up to 30 minutes before the study drug administration. All other samples will be collected as close as possible to the scheduled time point within windows as specified in the Schedule of Events (Appendix 13.1). Actual sampling times for each subject will be recorded in the subject's eCRF and individual source documents.

Subjects will be required to refrain from intense exercise the day prior to the assessment, to fast overnight for 8 hours prior to the blood samples being taken for assessment, and to visit the study site in the morning for PK assessment.

6.3 Pharmacodynamics

Concentrations of the bone turnover marker (sCTX) will be measured from fasting serum samples in the Main Treatment Period and Transition/Safety Follow-Up Period at the time points specified in the Schedule of Events (Appendix 13.1). If the blood sample is unable to be analysed or is missing at a certain time point, some blood samples collected for PK or immunogenicity assessment at the same time point can be used for PD assessment if PK or immunogenicity assessment is completed for the time point and after discussion and agreement from mAbxience. This will be performed if the storage conditions are similar, the volume of the samples is sufficient, and the date/time of sample collection is known and is suitable for PD analysis. Analysis will be performed at the central laboratory using validated bioanalytical methods.

The total volume of blood collected for PD assessments is discussed in the laboratory manual. The sample collection tube may be changed during the study, and details will be provided in the laboratory manual.

All samples will be collected as close as possible to the scheduled time point. Actual sampling times for each subject will be recorded in the subject's eCRF and individual source documents.

Subjects will be required to refrain from intense exercise the day prior to the assessment, to fast overnight for 8 hours prior to the blood samples being taken for assessment, and to visit the study site in the morning for PD assessment.

6.4 Immunogenicity Assessments

The immunogenicity of MB09 and EU-Prolia will be assessed by antidrug antibody and neutralising antibody test in a validated immunoassay. Blood samples for immunogenicity assessments in the Main Treatment Period and Transition/Safety Follow-Up Period will be collected at the time points specified in the Schedule of Events (Appendix 13.1).

Blood samples for immunogenicity for subjects with immune-related adverse events will be obtained on the onset date of immune-related adverse events.

The total volume of blood collected for PD assessments is discussed in the laboratory manual. The sample collection tube may be changed during the study and details will be provided in the laboratory manual.

Predose samples (Day 1, Month 6 and Month 12) will be collected up to 30 minutes before the study drug administration. All other samples will be collected as close as possible to the scheduled time point within windows as specified in the Schedule of Events (Appendix 13.1). Actual sampling times for each subject will be recorded in the subject's eCRF and individual source documents.

Subjects will be required to refrain from intense exercise the day prior to the assessment, to fast overnight for 8 hours prior to the blood samples being taken for assessment, and to visit the study site in the morning for immunogenicity assessment.

6.5 Safety Assessments

Safety assessments will be performed as shown in the Schedule of Events (Appendix 13.1) on adverse events (including serious adverse events), adverse events of special interest (injection site reaction, drug-related hypersensitivity/allergic reaction monitoring, infection,

hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction and atypical femoral fracture), vital sign assessments, body weight, height, body mass index, lateral spine radiography (screening only; radiographs will be performed as required for suspected new clinical fractures), ECG, physical examination, clinical laboratory analyses, and prior and concomitant medications. Hepatitis B virus, HCV, HIV-1/HIV-2, SARS-CoV-2, and follicle-stimulating hormone testing, and NYHA Functional Classification (will be performed only in subjects with heart failure) will be assessed to determine subjects' eligibility. Further SARS-CoV-2 tests will be performed as required. See the Schedule of Events (Appendix 13.1) for further details.

6.5.1 Adverse Events

6.5.1.1 Definitions

6.5.1.1.1 Adverse Events

The investigator is responsible for reporting all adverse events that are observed or reported during the study, regardless of their relationship to the study drug or their clinical significance.

An adverse event is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to the study drug. Subjects will be instructed to contact the investigator at any time after randomisation if any symptoms develop.

Any new condition noted at or after screening up to baseline (ie, before administration of the first dose of the study drug) will be regarded as an adverse event, but not a treatment-emergent adverse event. A treatment-emergent adverse event is defined as any event not present before exposure to the study drug or any event already present that worsens in either intensity or frequency after exposure to the study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen are not considered adverse events. Laboratory results of disease/disorders being studied, medical/surgical procedures are not an adverse event but rather the condition/event that leads to it are defined as an adverse event.

Any abnormal laboratory test results (haematology, clinical chemistry or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital sign measurements), including those that worsen from baseline or are clinically significant in the medical and scientific judgement of the investigator will be recorded as adverse events or serious adverse events if they fulfil the following:

- Results in discontinuation from the study.
- Requires treatment or any other therapeutic intervention.
- Requires further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality).
- Are clinically significant as evaluated by the investigator.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, will not be reported as adverse events or serious adverse events. Disease progression of postmenopausal osteoporosis will not be recorded as an adverse event or serious adverse event; however, any new fractures confirmed by the central imaging vendor will be recorded as adverse events or serious adverse events (Section 6.1.1).

Medical intervention such as surgery, diagnostic procedures and therapeutic procedures are not adverse events, but the action taken to treat the medical condition. They will be recorded as treatment(s) of the adverse events. The event term of primary cause will be recorded and reported instead of the term of surgery, diagnostic procedure, or therapeutic procedure.

6.5.1.1.2 Serious Adverse Events

A serious adverse event is defined as any event that:

- Results in death.
- Is immediately life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

Medical and scientific judgement will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

Adverse events associated with hospitalisation (over 24 hours) or prolongation of hospitalisation are considered as serious adverse events. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, from medical floor to a coronary care unit, from neurological floor to a tuberculosis unit).

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating clinical adverse event is not in itself a serious adverse event. Examples include the following:

- Admission for treatment of a pre-existing condition not associated with the development of a new adverse event or worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment laboratory abnormality).
- Social admission (eg, subject has no place to sleep).
- Purely for convenience (eg, for easier performance of study assessments).
- Administrative admission (eg, for yearly physical examination).
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol).
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery).
- Hospitalisation for observation without a medical adverse event.
- Pre-planned treatments or surgical procedures; these will be noted in the baseline documentation for the entire protocol and/or for the individual subject.

- Hospitalisation solely due to disease progression without any other adverse events as decided by the investigator.

6.5.1.2 Adverse Events of Special Interest

An adverse event of special interest (serious or nonserious) is defined as an adverse event or serious adverse event of scientific and medical concern specific to mAbxience's product or programme.

Adverse events of interest will be appropriately reported using the same processes as those for reporting adverse events or serious adverse events (ongoing monitoring and rapid communication by the investigator to mAbxience (EMA 2011)).

The following adverse events are considered as adverse events of special interest:

- Injection site reaction.

Injection site will be observed for potential injection site reaction after study drug administration and assessed based on CTCAE Version 5.0. All adverse events related to injection site reaction including cellulitis, erythema, itching, haemorrhage, pain and swelling will be reported.

- Drug-related hypersensitivity/allergic reaction.

All adverse events related to hypersensitivity/allergic reactions including anaphylaxis after study drug administration will be reported. Symptoms including but not limited to hypotension, dyspnoea, throat tightness, facial and upper airway oedema, pruritus and urticaria will be reported.

- Infection.

All adverse events related to infections including, but not limited to, urinary tract infection, upper respiratory tract infections, skin infections including but not limited to erysipelas and cellulitis, abdomen infection and ear infection will be reported.

- Hypocalcaemia.

All adverse events related to hypocalcaemia including, but not limited to, paraesthesia or muscle stiffness, twitching, spasms and muscle cramps, QT interval prolongation, tetany, seizures and altered mental status will be reported.

- Osteonecrosis of the jaw.

All adverse events related to osteonecrosis of the jaw including, but not limited to, jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration and gingival erosion will be reported.

- Dermatologic reaction.

All adverse events related to dermatologic reactions including, but not limited to, eczema and rashes will be reported.

- Atypical femoral fracture.

All adverse events related to atypical femoral fractures, including symptoms of new or unusual thigh, hip or groin pain, will be reported.

6.5.1.2.1 Suspected Unexpected Serious Adverse Events

A SUSAR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, investigator's brochure for an unapproved investigational medicinal product).

6.5.1.3 Eliciting and Documenting Adverse Events

At every study visit, subjects will be asked a standard nonleading question to elicit any medically-related changes in their well-being. The condition of the subject will be monitored throughout the study for any signs or symptoms. In addition to the subject's observations, adverse events identified from any study data (eg, laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are relevant to subject safety, will be documented on the adverse event page in the eCRF.

All adverse events will be assessed from the time the subject signs the ICF until 6 months after the last dose of study drug, regardless of the relationship to the study drug.

After the last End of Study visit, if the investigator learns of any additional serious adverse events or serious adverse drug reactions that occur while the subject was on the study or after study completion, the investigator will communicate this to mAbxience or its designee. If the investigator learns of any serious adverse event, including a death, at any time after a subject

has been discontinued from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify mAbxience.

6.5.1.3.1 Assessment of Severity

The severity, or intensity, of an adverse event refers to the extent to which an adverse event affects the subject's daily activities. The intensity of the adverse event will be rated using the following CTCAE grading criteria Version 5.0.

Grade 1:	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate: minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living.
Grade 3:	Severe: medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limited self-care activities of daily living.
Grade 4:	Life-threatening consequences: urgent intervention indicated.
Grade 5:	Death related to adverse event.

The investigator will assess the maximum intensity that occurred over the duration of the event. If an adverse event changes from nonserious to serious, a new serious adverse event needs to be reported noting the time of that transition. Adverse events characterised as intermittent do not require documentation of onset and duration of each episode.

6.5.1.3.2 Assessment of Causality

The investigator's assessment of an adverse event's relationship to the study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an adverse event, the event should be reported.

The relationship or association of the study drug in causing or contributing to the adverse event will be characterised using the following classification and criteria:

Unrelated: There is no association between the study drug and the reported event.

Possible: Treatment with the study drug caused or contributed to the adverse event, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: A reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgement based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: A definite causal relationship exists between drug administration and the adverse event, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is readministered.

6.5.1.4 Reporting Adverse Events

The adverse event reporting period for safety surveillance begins upon enrolment of the subject (ie, date of the signature of the ICF) and continues until 6 months after the last dose of study drug. All adverse events reported or observed during the study will be recorded on the adverse event page in the eCRF. Information to be collected includes the following:

- Event term.
- Time and date of onset.
- Investigator-specified assessment of severity and relationship to the study drug.
- Time and date of resolution of the event.
- Seriousness.
- Any required treatment or evaluations.
- Outcome.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states of the concurrent illness (ie, other than the study indication of osteoporosis) must also be reported. All adverse events will be followed to adequate resolution. The MedDRA will be used to code all adverse events.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an adverse event. However, if it deteriorates at any time during the study, it should be recorded as an adverse event.

6.5.1.4.1 Reporting Serious Adverse Events

Any adverse event that meets serious adverse event criteria (Section 6.5.1.1.2), whether or not considered causally related to the study drug or to study procedure(s), must be reported. All serious adverse events will be recorded in the eCRF within 24 hours of discovery.

In case the eCRF is inaccessible, the investigator must report all serious adverse events to mAbxience's Pharmacovigilance Department immediately (ie, within 24 hours of discovery) via the serious adverse event reporting form to:

Name of Department: Pharmacovigilance

Address: mAbxience [redacted].

Serious Adverse Event Hotline: [redacted]

Serious Adverse Event Fax line: [redacted]

E-mail: [redacted]

Data entry will be completed in the remote data capture system by the investigator within 24 hours of awareness of a serious adverse event. In the event that this is not possible (eg, system failure or access problems), the study site will complete a serious adverse event report form and e-mail/fax it to mAbxience's Pharmacovigilance Department within 24 hours of awareness of the event. The remote data capture system will be updated as soon as it is available. If the subject is hospitalised during a serious adverse event or because of a serious

adverse event, a copy of the hospital discharge summary will be faxed to mAbxience's Pharmacovigilance Department as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the principal investigator or subinvestigator. All serious adverse events (regardless of relationship to the study drug) will be followed up until satisfactory resolution or until the principal investigator or subinvestigator deems the event to be chronic or not clinically significant or the subject to be stable.

mAbxience has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. mAbxience will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IEC/REC, and investigators.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information from mAbxience will review and then file it as appropriate and will notify the IEC/REC, if appropriate according to local requirements.

6.5.1.4.2 Reporting Suspected Unexpected Serious Adverse Reactions

mAbxience will promptly evaluate all SUSARs and nonserious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IECs/RECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, mAbxience will assess the expectedness of these events using applicable reference documents (eg, mAbxience 2021).

mAbxience will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by mAbxience as needed.

6.5.1.5 Follow-Up of Subjects Reporting Adverse Events

All adverse events must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, the event is considered to be stable, or the subject is lost to follow-up.

6.5.2 Clinical Safety Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected at the time points specified in the Schedule of Events (Appendix 13.1). The total volume of blood collected for clinical safety assessments is discussed in the laboratory manual. The sample collection tube may be changed during the study, and details will be provided in the laboratory manual.

Subjects will be required to refrain from intense exercise the day prior to the assessment, to fast overnight for 8 hours prior to the blood samples being taken for assessment, and to visit the study site in the morning for clinical laboratory assessments.

Clinical laboratory test samples will be analysed at the central laboratory. In the case that usage of the central laboratory is limited due to unforeseen changes in the COVID-19 pandemic, certain safety laboratory assessments may be performed at a local laboratory with the pre-approval of mAbxience. The investigator should assess the available results with regard to clinically relevant abnormalities. Safety laboratory results should be signed and dated and retained at the investigator site as a source of data for laboratory variables.

All samples will be collected as close as possible to the scheduled time point. Actual sampling times for each subject will be recorded in the subject's eCRF and individual source documents. Note: Blood samples for clinical chemistry are recommended to be taken prior to study drug administration for the monitoring of albumin-adjusted total serum calcium levels (see Section 5.2.2.1 for further information).

The following clinical laboratory analyses will be performed.

Haematology:	Haemoglobin, haematocrit, red blood cell count, white blood cell count with differential count, absolute neutrophil count, absolute lymphocyte count and platelet count.
Clinical Chemistry:	Albumin, albumin-adjusted total serum calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, chloride, total cholesterol, high-density lipoprotein cholesterol, creatine kinase, creatine kinase-myocardial band isoenzyme, creatine phosphokinase, creatinine, gamma-glutamyl transferase, glucose, lactate dehydrogenase, triglycerides, magnesium, phosphate, potassium, sodium, total bilirubin, direct bilirubin, total protein, uric acid, troponin I, thyroid-stimulating hormone, parathyroid hormone (intact), follicle-stimulating hormone and serum 25-OH vitamin D.
Coagulation:	INR and aPTT.
Urinalysis:	Colour, pH, specific gravity, glucose, ketones, leukocytes, nitrite, protein, bilirubin, urobilinogen, occult blood and microscopic examination (only if urinalysis dipstick results are abnormal).

Clinical monitoring of albumin-adjusted total serum calcium, serum 25-OH vitamin D and mineral levels (magnesium, phosphate) will be performed. Any sign and symptoms of hypocalcaemia will be closely sought and adequately treated at the investigator's discretion.

Albumin-adjusted total serum calcium level will be calculated using the following formula: Corrected calcium (mg/dL) = measured total calcium (mg/dL) + 0.8 (4.0 − serum albumin [g/dL]), where 4.0 represents the average albumin level.

If the albumin-adjusted total serum calcium level is calculated using mg/dL unit, it will be adjusted for SI units using the following formula: Corrected calcium (mmol/L) = total calcium (mmol/L) + 0.02 (40 – serum albumin [g/L]).

Any abnormal laboratory test results (haematology, clinical chemistry or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital sign measurements), including those

that worsen from baseline or are clinically significant in the medical and scientific judgement of the investigator are to be recorded as adverse events or serious adverse events.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as adverse events or serious adverse events.

The investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study. If the laboratory reports are not transferred electronically, the values must be filed with the source information (including reference ranges). In most cases, clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and mAbxience should be notified.

All protocol-required laboratory assessments, as defined in Appendix 13.1, must be conducted in accordance with the laboratory manual and the Schedule of Events. If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, serious adverse event or adverse event), then the results must be recorded in the eCRF.

6.5.2.1 Hepatitis B Virus, Hepatitis C Virus, Human Immunodeficiency Virus Subtype-1 and Subtype 2 and SARS-CoV-2

At the screening visit, subjects will be screened for HBV surface antigen, HCV antibody and HIV-1/HIV-2 antibody. If a positive surface antigen test result is obtained for hepatitis B, a confirmatory test is required. In the case of a positive HCV test, an HCV viral RNA load test will be performed as a confirmatory test. In the case of a positive HIV-1/HIV-2 test result, a confirmatory test will be performed. Hepatitis B virus, HCV and HIV-1/HIV-2 analyses will be performed at the central laboratory. Refer to the laboratory manual for further details.

At the screening visit, a COVID-19 test will be performed. Subjects who have a COVID-19 infection will be allowed to be rescreened on the basis that they have a confirmatory negative COVID-19 test result and have completely recovered from COVID-19 before being entered into the study. In the case that a subject is required to be rescreened within 28 days of the initial screening no additional tests are required to be performed. In the case that a subject is required to be rescreened after 28 days from the initial screening, all screening procedures/tests are required to be repeated. Systematic COVID-19 screening tests will be performed locally based on the site guidelines and on the investigator's discretion throughout the study period. If COVID-19 is confirmed after randomisation, the investigator will discuss case-by-case with mAbxience and the medical monitor. If the subject has contact with COVID-19 infected patients within 14 days following any site visit, the investigator will re-assess the visit schedule following the site and/or local regulatory guidelines.

Further details on subjects who test positive for SARS-CoV-2 are provided in Appendix 13.3.

6.5.2.2 Follicle-Stimulating Hormone

Women of childbearing potential will not be eligible for enrolment in this study. To confirm postmenopausal status, follicle-stimulating hormone levels will be measured at screening, which should be ≥30 mIU/mL with at least 12 consecutive months since spontaneous amenorrhea. Note: Women with surgical menopause will not have their postmenopausal status confirmed with follicle-stimulating hormone test but confirmation will be via their medical history.

6.5.3 Physical Examinations

Investigators will carefully evaluate subjects for any indication of injection site reaction, hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction and atypical femoral fracture and treatment will be indicated in accordance with the investigator's medical judgement. Especially, a dental examination with appropriate preventive dentistry will be performed in subjects who develop risk factors for osteonecrosis of the jaw while on-study. Physical examination will be performed at the time points specified in the Schedule of Events (Appendix 13.1).

Information about the physical examination will be recorded by the investigator or designee in the eCRF and source documents. Any abnormalities will be recorded in the source

documents. Clinically significant findings and illnesses reported after the start of the study that meet the definition of an adverse event will be recorded in the eCRF and source documents.

At the screening, baseline (Day 1), Month 6, Month 12 and Transition Period Month 6 (End of Study) visits, a complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. A symptom-specific physical examination will be performed for other study visits. Clinically significant findings and illnesses reported after the start of the study that meet the definition of an adverse event will be recorded in the eCRF and source documents.

6.5.4 Vital Signs

Vital signs, weight and height measurement and body mass index calculation will be performed at the time points specified in the Schedule of Events (Appendix 13.1). Vital signs (including systolic and diastolic blood pressures, heart and respiratory rates and body temperature) will be measured after 5 minutes of rest (sitting) (once at predose and once at postdose for Day 1, Month 6 and Month 12 visits, and once for all other visits). Vital sign measurements will be monitored before (within 15 minutes) and after the study drug administration (1 hour [±10 minutes]) as part of the hypersensitivity/allergic reaction monitoring (Section 6.5.6.3).

Subjects will be instructed to measure their axillary body temperature before visiting the site. At site, the subject's body temperature will be measured before the administration of study drug. In the case of a body temperature above normal (>37.5ºC), the subject will not be administered study drug.

Body mass index will be calculated by subject's weight in kg divided by subject's height in m^2. All other measurements will be documented at each study site visit. Details will be recorded in both the eCRFs and source documents.

6.5.5 Electrocardiograms

A 12-lead ECG will be performed at the time points specified in the Schedule of Events (Appendix 13.1) at the study site after the subject has rested quietly for at least 5 minutes in a supine position. After the investigator reviews the ECG, if there are any ECG findings that will indicate cardiac insufficiency or QT prolongation, the subject will be referred to a

cardiologist to confirm the abnormality and to identify any cause or underlying pathology. If an ECG trace indicates an abnormality that is measured by the equipment but is deemed normal by the investigator, this should be clearly stated on the ECG trace as normal and signed and dated by the investigator or appropriately qualified designee. The investigator will report the event at any time if clinically indicated in the eCRF and source documents. Regardless of 12-lead ECG result, further evaluation with a cardiologist can be done depending on the investigator's discretion. PR interval, QRS complex duration, QT interval and QT interval corrected according to Fridericia's formula will be calculated.

6.5.6 Other Safety Assessments

6.5.6.1 Medical History, Disease History and Demographic Information

The medical history (general medical history and medication history), disease history of postmenopausal osteoporosis, fracture history and demographic information including gender, age, ethnicity, race and body mass index (kg/m^2) at screening (Visit 1) will be recorded in the subject's eCRF and the source documents.

6.5.6.2 Injection Site Reaction Monitoring

Injection site reactions will be assessed up to 1 hour (±10 minutes) after the End of Study drug administration, as specified in the Schedule of Events (Appendix 13.1). Injection site reactions will be graded per FDA guidance (DHHS 2007) as shown in Table 6-1.

Table 6-1 Local Reactions to Injected Study Drug

Local Reaction to Injected Study Drug	None (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalisation
Tenderness	None	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalisation
Erythema/Redness*	None	2.5 to 5 cm	5.1 to 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	None	2.5 to 5 cm and does not interfere with activity	5.1 to 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

*In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
**Indurations/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Details will be recorded in the source documents and severity (the worst grade from categories of pain, tenderness, erythema and swelling) would be collected in the eCRF as an AESI.

6.5.6.3 Hypersensitivity/Allergic Reaction Monitoring

Hypersensitivity/allergic reactions monitoring will be assessed before the start of the study drug administration (within 15 minutes) and at 1 hour (±10 minutes) after the end of the study drug administration, as specified in the Schedule of Events (Appendix 13.1), by additional vital sign measurements including blood pressure, heart and respiratory rates and body temperature. If subjects have signs and symptoms of hypersensitivity/allergic reactions at home (hives, difficulty breathing, or swelling of face, eyes, lips, or mouth or any

symptoms of cardiac origin), subjects or caregivers will be advised to call the study site or get immediate help.

In addition, hypersensitivity will be monitored by routine continuous clinical monitoring including subject-reported signs and symptoms. In case of hypersensitivity, emergency medication and equipment such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen and artificial ventilation must be available.

For subjects who experience or develop life-threatening treatment-related hypersensitivity/allergic reactions, the study drug must be stopped immediately. The subject should be permanently discontinued from the study drug and should be asked to complete the scheduled visits until the end of the Main Treatment Period at Month 12.

Details will be recorded in both the source documents and the eCRF.

6.5.6.4 New York Heart Association Functional Classification

The NYHA Functional Classification (Appendix 13.3) assessment for heart failure will be performed only in subjects with heart failure at screening to determine eligibility, as specified in the Schedule of Events (Appendix 13.1). Results will be recorded in both the eCRF and source documents.

6.6 Labelling, Storage, and Transportation of Samples

During the study, blood samples will be collected for PK, PD, immunogenicity and safety analyses. Details of sample storage and transportation will be provided in the laboratory manual.

6.6.1 Sample Labelling

Instructions for labelling of the sample tubes will be provided in the laboratory manual.

6.6.2 Sample Storage and Shipment

Where appropriate, the serum will be transferred into a sufficient number of transfer tubes for transport to assigned testing facilities. Primary and backup samples will be shipped to the central laboratory according to the laboratory manual, and primary samples will be shipped separately from the backup samples. Laboratory samples (excluding PK, antidrug antibody

and neutralising antibody samples) will be stored for up to 6 months after testing and analysis is completed. Samples for PK, antidrug antibody and neutralising antibody will be stored until the End of Study Clinical Study Report is released. After that, mAbxience can choose to store the samples for a longer duration or ship the samples to a specified location or dispose of the samples.

6.7 Prevention of Missing Data

The following steps will be implemented to prevent missing data (Fleming 2011).

- The investigators will be trained about the importance of subject retention.
- The consent form will include a statement educating subjects about the continued scientific importance of their data even if they discontinue study treatment early.
- There will be an option of partial withdrawal, so that subjects are encouraged to return to the Month 6 and Month 12 visit if they find the burden of study procedures too difficult.
- Several approaches will be implemented to retain subjects who fail to actively maintain contact with the investigator (eg, telephone calls to friends or family members, e-mails, offers for transportation to the clinic).

7 Statistical Considerations

The statistical analysis will be performed using SAS software Version 9.4 or later. The statistical methods for this study will be described in a detailed statistical analysis plan, which will be finalised before database lock at Month 12. Changes from analyses planned in this protocol will be documented in the statistical analysis plan. Any deviations from the planned analysis as described in the statistical analysis plan will be justified and recorded in the Clinical Study Report.

Data collected before and up to the end of the Main Treatment Period (Month 12) prior to the third administration of study drug will be analysed in the Primary Month 12 Analyses and will be reported in the Clinical Study Report.

Data collected before and up to the end of the Transition/Safety Follow-Up Period (Transition Period Month 6) will be analysed in the Final Analyses and will be reported in the End of Study Clinical Study Report Addendum.

Full details of the statistical methods will be described in the statistical analysis plan.

7.1 Estimands and Intercurrent Events

7.1.1 Intercurrent Events

The following ICEs are relevant in the treatment of postmenopausal women with osteoporosis by subcutaneous injection of study drug (MB09 or EU-Prolia every 6 months):

- **Discontinuation of study drug due to any reason,** though it will be helpful for sensitivity analyses to distinguish between discontinuations:
    - **Related to study drug or osteoporosis** which includes discontinuation due to lack of efficacy, tolerability issue or because the subject finds the subcutaneous administration uncomfortable or because the subject prefers to transition to another product.
    - **Not related to study drug or osteoporosis** which could be another medical condition requiring treatment, a logistical issue such as a house move or pandemic lockdown, or the burden or inconvenience of the study procedures (not related to any dissatisfaction with the study drug).

- Errors or deviations in dosing: this would include incorrect dose, incorrect study drug, incorrect route or dosing interval not 6 months (181 ± 10 days). Note: Study drug will be administered by the clinical staff to minimise the chance of error.
- Administration of any prohibited therapies or other osteoporosis medications.
- Adjustments to vitamin D or calcium supplements.
- Formation of antidrug antibodies.
- Death, though it will be helpful for sensitivity analyses to distinguish between deaths:
    - Related (probably or possibly) to the study drug or disease progression of osteoporosis;
    - Not related (even possibly) to the study drug or disease progression of osteoporosis (eg, due to an accident or comorbidity unrelated to osteoporosis and not related to any adverse event believed to be probably or possibly related to the study drug).

7.1.2 Estimands

Table 7-1 presents the primary objective with its estimands and rationale for strategies to address ICEs.

Table 7-1 Primary Objective and Estimands With Rationale for Strategies to Address Intercurrent Events

	Estimand 1a (Primary)	**Estimand 1b (Supportive)**
Estimand Description (summary below)	Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive two denosumab doses without any errors or deviations in dosing and without receipt of any prohibited therapies or other osteoporosis medications.	Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any prohibited therapies or other osteoporosis medications are taken.

	Estimand 1a (Primary)	**Estimand 1b (Supportive)**
Treatment Conditions of Interest	MB09 versus EU-Prolia	
Target Population	Postmenopausal women with osteoporosis	
Endpoint	Percentage change from baseline in lumbar spine bone mineral density (*%CfB* lumbar spine BMD) to Month 12 and taking *%CfB* value of zero for someone who dies.	
Population Level Summary	Difference between treatments in population mean *%CfB* BMD at Month 12.	
ICEs and Strategies to Handle ICEs	**Hypothetical strategy** for: • Discontinuation of study drug due to any reason (related or unrelated to study drug or osteoporosis). • Errors or deviations in dosing. • Administration of any prohibited therapies or other osteoporosis medications. **Treatment policy strategy** for: • Formation of antidrug antibodies. • Adjustments to calcium and vitamin D. **Composite strategy** for death.	**Treatment policy strategy** for: • Discontinuation of study drug due to any reason (related or unrelated to study drug or osteoporosis). • Errors or deviations in dosing. • Administration of any prohibited therapies or other osteoporosis medications. • Formation of antidrug antibodies. • Adjustments to calcium and vitamin D. **Composite strategy** for death.
Rationale	It is anticipated that the occurrence of each ICE will be balanced between groups since the biosimilar, MB09, should have similar properties to the EU-Prolia. Note that the treatment policy approach in the primary Estimand 1b requires **follow-up of subjects to measure BMD at Month 12 irrespective of whether they have taken any prohibited therapies or other osteoporosis medication or not received both doses.** It should be noted that Prolia has a good safety profile and it is anticipated that <1% of subjects will have tolerability issues or die during the year after first dose. The hypothetical strategy of Estimand 1a will require statistical modelling to estimate the difference that might exist in the scenario that those ICEs do not occur. Note: The formation of antidrug antibodies against EU-Prolia in the first year of treatment is not particularly common (<1%) and thus this ICE has not been specifically mentioned in the estimand and will be ignored in estimation approaches.	

[1] Women will not have been previously treated with denosumab but may have had prior treatment with bisphosphonates and will be co-administered calcium and vitamin D supplements.

Abbreviations: %CfB, percentage change from baseline; BMD, bone mineral density; EU-Prolia, EU-sourced Prolia; ICE, intercurrent event.

Note: The screening BMD assessment will be taken as the baseline BMD assessment.

7.2 Statistical Hypothesis

The statistical hypothesis associated with the difference in treatments for the primary efficacy analysis of %CfB in lumbar spine BMD at Month 12 is:

H0: ($\mu_{MB09} - \mu_{Prolia} \leq -1.45\%$) or ($\mu_{MB09} - \mu_{Prolia} \geq +1.45\%$)

H1: $-1.45\% < \mu_{MB09} - \mu_{Prolia} < +1.45\%$

where μ_{MB09} and μ_{Prolia} denote the true mean %CfB in lumbar spine BMD at Month 12 for MB09 and EU-Prolia, respectively.

7.3 Sample Size Determination

A sample size of 448 subjects (224 subjects on each of MB09 and EU-Prolia [Arm 2 Prolia-MB09 and Arm 3 Prolia-Prolia pooled] at Month 12) will achieve 85% statistical power for the demonstration of equivalence in the %CfB lumbar spine BMD at Month 12, based on the two one-sided 2.5% significance level and an equivalence margin of ±1.45%. In this sample size calculation, the common SD is assumed to be 4.5% and the true mean difference of %CfB is assumed to be zero. Therefore, allowing for a 15% dropout, 528 subjects will be randomised 2:1:1 to the MB09-MB09, Prolia-MB09 and Prolia-Prolia treatment arms.

A meta-analysis of three studies (Bone et al 2008, Cummings et al 2009, and McClung et al 2006) gave the pooled denosumab treatment effect 5.35% (95% CI: 4.83% to 5.87%). Based on the lower bound of the 95% CI, a 1.45% margin will preserve 70% of the treatment effect (0.3*4.83%).

7.4 Analysis Sets

The following analysis sets will be used in the statistical analyses.

7.4.1 Full Analysis Set

The FAS will consist of all randomised subjects who meet the eligibility criteria and receive at least one dose of study drug. Subjects from the FAS will be analysed under the treatment as randomised and will be used for supportive analyses for efficacy endpoints.

7.4.1.1 Modified Full Analysis Set

The term mFAS will be used to define the analysis data set which includes a data record at each time point for all subjects in the FAS but excludes data observed after the first occurrence of those ICEs where a hypothetical strategy is taken (eg, missing a dose, errors or deviations in dosing, or receipt of any prohibited therapies or other osteoporosis medication). Data in the mFAS will be analysed under the treatment as randomised and used as the primary analysis set for efficacy and PD.

7.4.1.2 Full Analysis Set for the Transition Period

The FAS-TP will consist of all randomised subjects in the SAF-TP who progressed to receive a dose of study drug at Month 12, fully meet eligibility criteria and have successfully tolerated the previous two doses of study drug.

7.4.1.3 Modified Full Analysis Set for the Transition Period

The term mFAS-TP will be used to define the analysis data set with a data record at each time for subjects in the FAS-TP but excludes data observed after the first occurrence of ICE.

7.4.1.4 Pharmacokinetic Analysis Sets

The PK Concentration Sets for the Main Treatment Period (PKCS) and for the Transition Period (PKCS-TP) are concentration observation-level sets which comprise all subjects who received at least one full dose of study drug (MB09 or EU-Prolia) in the respective period and exclude observations after relevant ICEs which impact PK (eg, missing a dose, errors or deviations in dosing or receipt of other therapies which also contain denosumab). These sets will be used for summaries of concentrations and troughs.

The PK Parameter Set (PKPS) for the Main Treatment Period comprises all subjects who have at least three measurable concentrations in PKCS, which must include Day 11 to allow for reliable estimation of both C_{max} and $AUC_{0\text{-}6\ months}$. The PK Parameter Set for the Transition Period (PKPS-TP) is defined similarly.

7.4.2 Safety Analysis Set

The SAF will consist of all randomised subjects who received at least one administration of study drug. The SAF will be used for all safety and immunogenicity analyses. In the SAF, subjects will be analysed per the actual treatment received.

7.4.3 Safety Analysis Set for the Transition Period

The SAF-TP will consist of all subjects in the SAF who progressed to receive a dose of study drug at Month 12, and so thereby enter the Transition Period. The SAF-TP will be used for all safety and immunogenicity analyses of the Transition Period (per the actual treatment received).

7.5 Description of Subgroups to be Analysed

Subgroup analyses will be performed for the following:

- Baseline lumbar spine BMD T-score (≤ -3.0 versus > -3.0 SD).
- Body mass index (<25 versus ≥25 kg/m^2).
- Age at study entry (≥55 to <68 years versus ≥68 to ≤80 years).
- Prior bisphosphonate medication use at study entry
  (prior use of bisphosphonates versus no prior bisphosphonate use).
- Body weight (≥50 to <70 kg versus ≥70 to ≤99.9 kg).
- Smoker (Yes/No).
- Region (Latin America/Europe).

7.6 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.4 or later. Continuous variables will be summarised using the mean, SD, median, minimum value and maximum value. Categorical variables will be summarised using frequency counts and percentages. Data will be listed in data listings.

Details of the statistical analyses, methods and data conventions are described in the statistical analysis plan.

All CIs presented will be 95% (two-sided) CIs. For primary efficacy, equivalence is demonstrated if the 95% CI falls entirely within predefined margins; this approach is equivalent to two one-sided tests at the 2.5% significance level.

7.6.1 General Considerations

Data collected in this study will be presented using summary tables, subject data listings and figures. For continuous variables, the number of observations, mean, SD, median, minimum and maximum will be presented. Categorical variables will be summarised by subject counts and percentages. For ordinal-scaled variables, a combination of presentations may be employed as appropriate: frequency and percentage of observations within a category and means and SDs of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on the N of the analysis set and number of subjects with missing data will also be included.

7.6.1.1 Descriptive Statistics for the Main Treatment and Transition/Safety Follow-Up Periods

The periods of the study will be summarised separately so that:

- In the Main Treatment Period, subjects will be summarised by treatment (MB09 versus Prolia) up to Month 12 (predose). The Prolia group will pool subjects from Arm 2 Prolia-MB09 and Arm 3 Prolia-Prolia.
- In the Transition/Safety Follow-Up Period, subjects will be summarised by treatment arm (MB09-MB09, Prolia-MB09, Prolia-Prolia) up to Transition Period Month 6.

In the text that follows, "treatment (arm)" will be used to refer to treatment or treatment arm depending on whether referring to the Main Treatment Period or Transition/Safety Follow-Up Period, respectively.

7.6.2 Overview of Statistical Methods: Estimation of Estimands and Sensitivity Analyses

Table 7-2 presents a summary of statistical methods including sensitivity analyses.

Table 7-2 Summary of Statistical Methods, Including Sensitivity Analyses

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 1a (Primary)	Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive two denosumab doses without any, errors or deviations in dosing and without receipt of any prohibited therapies or other osteoporosis medications.	mFAS	The composite endpoint defines any deaths as zero. mFAS removes data occurring after ICEs for which the hypothetical strategy is used (keeping all subjects in the FAS). For sensitivity [i], MI under MAR [ii] delta applied to imputation in the tipping point approach.	MMRM of *%CfB* BMD at Month 6 and Month 12 including terms for visit by treatment, baseline BMD (as a covariate), and classification variables for: age, body mass index and prior use of bisphosphonates. The estimated mean difference in *%CfB* will be presented with 95% CI at each time point. The 95% CI for the mean difference at Month 12 in *%CfB* BMD will be compared to margins of [-1.45, 1.45]. (See Section 7.6.3.1 for further details).	[i] MI under MAR approach will be applied to the mFAS (see Section 7.6.3.2.1 for further details). %CfB BMD at Month 12 from each multiply imputed data set will be analysed by MMRM and results pooled using Rubin's method. [ii] A tipping point analyses will be performed. First, MI under MAR will be used to impute missing data where a penalty will be added to the imputed %CfB values. The same penalty (delta) will be applied to anyone who dies. The tipping point will consider delta1 and delta2 for the Prolia and MB09, respectively in a matrix of delta so that tipping points for both the upper and lower margins are considered (see Section 7.6.3.2.2 for further details). **Supplementary:** MMRM analysis of log transformed data (see Section 7.6.3.5 for further details).
Estimand 2a	Similarly for lumbar spine BMD at 6 months	mFAS	As above	As above	As above for [i] MI under MAR, and supplementary MMRM on log data.

Table 7-2 Summary of Statistical Methods, Including Sensitivity Analyses

Estimand Label	Estimand Description	Main Estimation: Analysis Set	Main Estimation: Imputation/Data/ Censoring Rules	Main Estimation: Analysis Model/Method	Sensitivity Analysis
Estimand 1b (Supportive)	Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviation in dosing and whether any prohibited therapies or other osteoporosis medications are taken.	FAS	The composite endpoint defines *%CfB* of zero for anyone who dies. For the main analysis, observed data will be analysed without any imputation. For sensitivity [i], MI under MAR. [ii] offset applied to "treatment failures" to be centred around baseline.	ANCOVA of *%CfB* BMD at Month 12 and including terms for treatment, baseline BMD (as a covariate) and classification variables for: age, body mass index and prior use of bisphosphonates. The estimated mean difference in *%CfB* BMD will be presented with 95% CI (see Section 7.6.3.3 for further details).	[i] MI will impute any missing BMD data under MAR by treatment (see Section 7.6.3.2.1 for further details). [ii] A "treatment-failure" approach will be taken to anyone who discontinues treatment for a reason related to study drug or osteoporosis or who take any prohibited therapies or other osteoporosis medication so that imputed values from MI under MAR are adjusted to be centred around baseline (see Section 7.6.3.4.1 for further details). **Supplementary:** ANCOVA analysis of log transformed data (see Section 7.6.3.5 for further details).
Estimand 2b (Supportive)	Similarly for lumbar spine BMD at 6 months.	FAS	The composite endpoint defines any deaths as zero.	ANCOVA of *%CfB* BMD at Month 6 as above.	As above for [i] only. **Supplementary:** ANCOVA analysis of log transformed data (see Section 7.6.3.5 for further details).

Table 7-2 Summary of Statistical Methods, Including Sensitivity Analyses

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 3a-4a	Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB (zero is taken for anyone who dies) in* • *(3a) hip BMD after 6 and 12 months.* • *(4a) femur neck BMD after 6 and 12 months.* In postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive scheduled denosumab dose(s) without any errors or deviations in dosing and without receipt of any prohibited therapies or other osteoporosis medications are taken.	mFAS	The composite endpoint defines *%CfB* of zero for anyone who dies. The mFAS removes data occurring after ICEs for which the hypothetical strategy is used (keeping all subjects in the FAS).	As per Estimand 1a and 2a for lumbar spine BMD, MMRMs will be fitted to hip BMD and to femur neck *%CfB* BMD at Month 6 and Month 12 and these will be of the same form including terms for visit by treatment, baseline BMD and strata as classification variables. (See Section 7.6.4.1 for further details).	None.

Table 7-2 Summary of Statistical Methods, Including Sensitivity Analyses

Estimand Label	Estimand Description	Main Estimation: Analysis Set	Main Estimation: Imputation/Data/ Censoring Rules	Main Estimation: Analysis Model/Method	Sensitivity Analysis
Estimand 3b-4b	Difference in means (MB09 minus EU-Prolia) in • *(3b) hip BMD after 6 and 12 months.* • *(4b) femur neck BMD after 6 and 12 months.* (where *%CfB* of zero is taken for anyone who dies) in postmenopausal women[1] with osteoporosis treated with scheduled denosumab dose(s) every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any prohibited therapies or other osteoporosis medications are taken.	FAS	The composite endpoint defines any deaths as zero. Observed data will be analysed without any imputation.	ANCOVA of *%CfB* BMD for each endpoint by time point and including terms for treatment, baseline BMD, and strata as classification variables. The estimated mean difference in *%CfB* will be presented with 95% CI. (See Section 7.6.4.2 for further details).	None.

Table 7-2 Summary of Statistical Methods, Including Sensitivity Analyses

Estimand Label	Estimand Description	Main Estimation: Analysis Set	Main Estimation: Imputation/Data/ Censoring Rules	Main Estimation: Analysis Model/Method	Sensitivity Analysis
Estimand 5	Ratio of geometric means (MB09/EU-Prolia) in *sCTX* $AUEC_{0\text{-}6\ months}$ in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming all women receive their first denosumab dose without any errors in dosing and without receipt if any prohibited therapies or other osteoporosis medications up to 6 months after the first dose. Additional summary: Mean difference in *sCTX* at 11 days; 1, 3 and 6 months after the first dose; and 6 months after the second dose of study drug.	mFAS	Interpolation/extrapolation will be used to calculate AUEC but will require at least baseline and three post-dose time points.	ANCOVA model on log transformed data including log transformed baseline *sCTX* as a continuous covariate with stratification variables included as classification factors. Back transformation of mean differences will give the ratio of geometric means(MB09/EU-Prolia) with 95% CI. (See Section 7.6.5 for further details).	**Supplementary:** MMRM on the unlogged *sCTX* allowing for different variability at each time point up to Month 12. The least square means and differences with 95% CI will be plotted over time. An estimate statement will be used to calculate a weighted average across the scheduled time points where the weights correspond to the weights used in calculating AUEC. Thus, this will give an estimate of mean AUEC and difference between mean AUEC with 95% CI. (See Section 7.6.5 for further details).

[1] Women will not have been previously treated with denosumab but may have had prior treatment with bisphosphonates and will be co-administered calcium and vitamin D supplements.

Abbreviations: %CfB, percentage change from baseline; ANCOVA, analysis of covariance; AUEC, area under the effect curve; $AUEC_{0\text{-}6\ months}$, area under the effect curve from zero to 6 months; BMD, bone mineral density; CI, confidence interval; EU-Prolia, EU-sourced Prolia; FAS, Full Analysis Set; ICE, intercurrent event; MAR, missing at random; mFAS, Modified Full Analysis Set; MI, multiple imputation; MMRM, mixed model for repeated measures; sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen.

Note: The screening BMD assessment will be taken as the baseline BMD assessment.

7.6.3 Analysis of Primary Efficacy Endpoint

7.6.3.1 Main Estimation of Estimand 1a (Primary)

For the primary efficacy analysis, an MMRM will be fitted to the composite %CfB lumbar spine BMD at Month 6 and Month 12 on the mFAS. The MMRM will include terms for visit by treatment, with stratification variables (age, body mass index and prior use of bisphosphonates) included as classification factors and baseline BMD included as a continuous covariate. Note: Baseline BMD at the lumbar spine is included as a covariate rather than including BMD T-score as a classification factor. Subject will be included as a random effect.

The estimated mean difference in %CfB lumbar spine BMD will be presented with 95% CI at each time point.

The estimated mean difference in %CfB lumbar spine BMD at Month 12 will be presented with 95% CI and equivalence concluded if this falls within predefined equivalence margins of [-1.45%, 1.45%].

Note: The main analysis method is on the mFAS and therefore does not use data after any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications.

7.6.3.2 Sensitivity Analysis of Primary Efficacy Endpoint

Two sensitivity approaches will be performed:

1. A multiply imputed data set produced under MAR as explained below in Section 7.6.3.2.1 will be applied to the mFAS. In each multiply imputed data set, all subjects in the FAS will have complete data and an indicator variable will be derived to indicate if data are observed or imputed. The composite %CfB lumbar spine BMD will be calculated as a post processing step from BMD values.

2. "Sensitivity using tipping point" will assess the robustness of results in both of the one-sided hypotheses by adding penalties in both directions to all missing data (see Section 7.6.3.2.1).

7.6.3.2.1 Multiple Imputation Model Under Missing at Random

Note that the composite endpoint of %CfB lumbar spine BMD is defined as zero for anyone who dies. In the case of MI, this will be applied after the MI and replace any imputed values.

Multiple imputation will be used to produce 30 multiply imputed data sets so that any missing BMD data at Month 6 or Month 12 are imputed under MAR, by treatment. This approach will be applied to both the mFAS (for Estimand 1a) and FAS (for Estimand 1b). Note: The mFAS excludes data after relevant ICEs and treats it as missing.

The MI approach will comprise of two steps:

1. Any intermittent missing data at Month 6 (ie, where Week 0 and Month 12 data are available) will be imputed using a Markov Chain Monte Carlo approach, using the impute = monotone option in SAS Version 9.4 (or higher) PROC MI.

2. A single imputation will be performed on each of the 30 multiply imputed data sets from Step 1 by treatment. This step will use a monotone regression approach.

The MI model will include continuous terms for age, body mass index, BMD at Week 0, Month 6 and Month 12, total number of doses received and indicator variables for prior use of bisphosphonates.

Full details of the MI models will be provided in the statistical analysis plan.

7.6.3.2.2 Sensitivity Using Tipping Point

Multiple imputation under MAR should produce results close to MMRM and ANCOVA analysis of observed data. The tipping point approach tests the robustness of results from MI assuming MAR by adding a penalty.

A penalty will be added to the Month 12 imputed %CfB lumbar spine BMD values (but not to data observed). The same penalty (delta) will be applied to anyone who dies for related reasons. The tipping point will add penalties of delta1 and delta2 to %CfB BMD values for EU-Prolia and MB09, respectively, in a matrix of values (delta1 = -6 to 6 by delta2 = -6 to 6 in steps of 1.5). For each combination of delta values, ANCOVA is performed for each multiply imputed dataset and then result pooled using Rubin's method. Note: That both positive and negative values of delta are tested in order to evaluate the tipping point of where

the 95% CI for the mean difference in %CfB BMD fails to meet each of the lower and upper bounds of the equivalence margins of [-1.45, 1.45].

7.6.3.3 Main Estimation of Estimand 1b (Supportive)

The supportive Estimand 1b requires that study conduct has made a good effort to follow-up on subjects particularly after ICEs.

In order to estimate Estimand 1b, an ANCOVA will be fitted to the composite %CfB lumbar spine BMD at Month 12 on the FAS including terms for treatment, with stratification variables (age, body mass index and prior use of bisphosphonates) included as classification factors and baseline BMD included as a continuous covariate. Note: Baseline BMD at the lumbar spine is included as a covariate rather than including BMD T-score as a classification factor.

The estimated mean difference in %CfB lumbar spine BMD will be presented with 95% CI.

7.6.3.4 Sensitivity Analysis of Estimand 1b (Supportive)

Two sensitivity approaches will be performed:

The same MI under MAR approach will be applied to the FAS (see Section 7.6.3.2.1).

1. Composite %CfB BMD at Month 12 from each multiply imputed data set will be analysed by ANCOVA and results pooled using Rubin's method.

2. "Sensitivity using treatment-failure penalty" will assess the robustness of results by assuming treatment failures return to levels around baseline (see Section 7.6.3.4.1).

Both sensitivity approaches start with a multiply imputed data set produced under MAR as explained above in Section 7.6.3.2.1.

7.6.3.4.1 Sensitivity Using Treatment-Failure Penalty

A "treatment-failure" approach will be taken for any subject with missing data at Month 12 who discontinues treatment for a reason related to study drug or osteoporosis or who takes any prohibited therapies or other osteoporosis medication so that it is assumed that the subject would return to around baseline levels. In order to allow for a reasonable level of

uncertainty in the imputed values, the imputed data from the MI under MAR are adjusted by an individual offset so that %CfB BMD values for a subject will be centred around zero. Thus, we calculate an alternative %CfB-TF defined as %CfB minus offset where offset is calculated for each individual as the mean of that individual's %CfB values (imputed under MAR). No offset is applied to observed data or deaths (deaths have composite %CfB BMD defined as zero). An ANCOVA is performed for each multiply imputed dataset and then results pooled using Rubin's method in order to present the difference in mean %CfB with 95% CI.

7.6.3.5 Supplementary Analysis of Primary Efficacy Endpoint

In order to investigate assumptions of normality, the log transformed BMD as a ratio of baseline will be analysed in a similar MMRM model to the main analysis but with baseline covariate as the log BMD (using the mFAS). The least squares means and difference will be back-transformed to present geometric mean ratios of baseline, and 95% CI for the ratio of geometric means (MB09/EU-Prolia). Note: For anyone who dies, no change from baseline will be assumed (BMD ratio of baseline of 1). Residual plots will be produced and compared to the main analysis.

Similarly, the ANCOVA analysis on the FAS will be performed on log transformed data as supplementary analysis for Estimand 1b.

7.6.4 Analysis of Key Secondary Efficacy Endpoints

7.6.4.1 Main Estimation of Hypothetical Estimand 2a-4a

The MMRM as per the main analysis of the primary endpoint (see Section 7.6.3.1) will be used to analyse composite endpoint of %CfB (zero is taken for anyone who dies) on the mFAS in:

- Lumbar spine BMD after 6 months.
- Hip BMD after 6 and 12 months.
- Femur neck BMD after 6 and 12 months.

7.6.4.2 Main Estimation of Treatment Policy Estimand 2b-4b

An ANCOVA (see Section 7.6.3.3) on the FAS will be used to analyse the composite endpoint of %CfB (zero is taken for anyone who dies) in:

- Lumbar spine BMD after 6 months.
- Hip BMD after 6 and 12 months.
- Femur neck BMD after 6 and 12 months.

7.6.4.3 Summary of Non-Traumatic Fractures

Any incidence of new non-traumatic fractures up to and including Month 12 will be summarised.

7.6.5 Analyses of Key Secondary Pharmacodynamic Endpoints

An sCTX $AUEC_{0\text{-}6\ months}$ will be calculated by the linear trapezoidal method provided there are at least baseline, and three postdose time points between Day 11 and Month 6, inclusive. Interpolation or extrapolation will be used if the last time point is not at exactly Day 182 and analysed on the log scale by ANCOVA (mFAS). The model will include log transformed baseline sCTX as a continuous covariate with stratification variables included as classification factors.

The estimated mean difference with 95% CI will be back-transformed to give the ratio of geometric means (MB09/EU-Prolia) with 95% CI.

A supplementary analysis will be performed to assess the impact of missing data. An MMRM will be fitted to the unlogged *sCTX* (mFAS) allowing for different variability at each time point (up to Month 12). The model will include fixed effect terms for visit by treatment, baseline sCTX and classification factors for each stratum. The least squares means and differences with 95% CI will be plotted over time. An estimate statement will be used to calculate a weighted average across the scheduled visits where the weights correspond to the weights used in calculating AUEC. Thus, this will give an estimate of mean AUEC and difference between mean AUEC with 95% CI.

Similarly, sCTX AUEC derived for the 6 months following the first dose in the Transition Period will be analysed (mFAS-TP) and comparisons will be made (Arm 2 Prolia-MB09/Arm 3 Prolia-Prolia and Arm 1 MB09-MB09/Arm 3 Prolia-Prolia).

7.6.6 Analyses of Secondary Pharmacokinetic Endpoints

The serum concentration-time data for denosumab will be summarised by time point (PKCS) and the PKPS analysed by non-compartmental analysis using Phoenix® WinNonlin® (Certara USA, Inc, Princeton, NJ) Version 8.0 or higher. C_{max}, $AUC_{0\text{-}6\ months}$ and troughs will be analysed on the log scale by ANOVA. The model will include treatment and stratification variables as classification factors.

The estimated mean difference with 95% CI will be back-transformed to give the ratio of geometric means (MB09/EU-Prolia) with 95% CI following the first dose in the Main Treatment Period. Similarly, parameters derived in the Transition Period will be analysed and comparisons will be made (Arm 2 Prolia-MB09/Arm 3 Prolia-Prolia and Arm 1 MB09-MB09/Arm 3 Prolia-Prolia). Further details will be provided in the statistical analysis plan.

7.6.7 Analyses of Secondary Immunogenicity Endpoints

Binding and neutralising serum denosumab antibodies will be summarised with summary statistics.

7.6.8 Safety Analyses

The Main Treatment Period and Transition Period will be analysed separately by treatment or treatment arm on SAF and SAF-TP, respectively.

In the Transition Period, changes from Month 12 and changes from baseline (Day 1) will be of interest.

7.6.8.1 Adverse Events

Treatment-emergent adverse events and serious adverse events recorded during the study will be summarised by system organ class, preferred term and treatment (arm), and will include the total number of events with number and percentage of subjects with adverse events.

Adverse events and medical history will be coded using the most current version of MedDRA.

Summaries of the number and percentage of subjects (and number and percentage of events) for study drug-related adverse events, severe adverse events, serious adverse events, adverse events with an outcome of death and adverse events leading to discontinuation of the study drug will be provided by treatment (arm).

Incidence and grade of adverse events of special interest including injection site reaction, drug-related hypersensitivity/allergic reaction monitoring, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction and atypical femoral fracture at each dosing visit will be summarised by treatment (arm). Injection site reactions will be summarised by severity (see Section 6.5.6.2 and Table 6-1).

7.6.8.2 Clinical Laboratory Assessments

Clinical safety laboratory data will be summarised descriptively by treatment (arm) and scheduled visits. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of changes from baseline for each parameter by treatment (arm). Summaries of safety laboratory parameters will include the first meaningful measurement of each scheduled assessment, but repeat assessments done at the same study time point will not be included in summary calculations (unless performed to provide missing data). Laboratory data will also be listed by treatment, subject and visit. Listings will include scheduled, unscheduled and repeat evaluations. A listing of markedly abnormal values will be generated. Shift tables by treatment (arm) will be provided when appropriate.

7.6.8.3 Vital Signs

Vital signs (blood pressure, heart rate, respiration rate and body temperature) and weight will be summarised by treatment (arm) at baseline and at each scheduled visit. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of change from baseline for each parameter by treatment (arm).

7.6.8.4 Physical Examinations

Abnormal physical examination findings that suggest a clinically significant worsening will be reported as adverse events and the number and percentage of subjects with normal or

abnormal results will be presented at scheduled visits by treatment (arm). Clinically significant findings noted prior to start of study drug treatment will be recorded as medical history and the number and percentage of subjects with clinically significant findings will be presented by treatment (arm).

7.6.8.5 Electrocardiograms

Electrocardiograms will be read locally. The number and percentage of subjects with normal or abnormal results will be presented at scheduled visits by treatment (arm). Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of changes from baseline for each parameter by treatment (arm).

The ECG data will also be presented in listings by subject and summarised by collection date and time.

7.6.8.6 Immunogenicity Analysis

Incidence of antidrug antibody to denosumab and neutralising antibodies will be summarised by treatment (arm) per time points as shown in the Schedule of Assessment (Appendix 13.1).

7.6.9 Other Analyses

7.6.9.1 Demographic and Baseline Disease Characteristics

If permitted by local regulation, the following demographic data will be summarised: age (in years, at the time of signing the ICF), race, ethnicity, height, weight and body mass index.

Demographics and baseline disease characteristics will be summarised descriptively by treatment (arm).

Subject disposition will be summarised by treatment (arm), including the reasons for discontinuation. The number of subjects in each analysis set will be displayed by treatment (arm).

7.6.9.2 Medical History

Medical history will be coded according to the latest version of MedDRA and will be summarised by system organ class and preferred term.

7.6.9.3 Study Drug Exposure

Study drug administrations will be summarised and listed by treatment (arm) up to Month 12 (predose) and up to Transition Period Month 6.

7.6.9.4 Prior and Concomitant Medications

The number and percentage of subjects with prior and concomitant medications will be tabulated by ATC Classification System of WHO drug, preferred term and treatment (arm). A medication's usage will be considered concomitant if it was started or continued after administration of the study medication. If the start date is missing, it will be assumed that the medication was used concomitantly. Details on handling partial dates (ie, year or only year and month) will be described in the statistical analysis plan.

7.6.9.5 Vitamin D and Calcium Intake

Vitamin D and calcium intake will be summarised and listed by treatment (arm).

7.6.9.6 Further Data

Further data (NYHA Functional Classification, lateral spine radiographs at screening [including radiographs performed for confirmation of suspected new clinical fractures], serology and follicle-stimulating hormone) will be listed (see Appendix 13.1).

7.6.10 Protocol Deviations

Protocol deviations will be summarised and listed. A separate listing for COVID-19-related protocol deviations will be prepared.

7.7 Handling of Missing Data

Study procedures will be in place to minimise missing data at Month 12 for the primary endpoint (%CfB BMD); for example, subjects who wish to withdraw from study treatment or take a prohibited therapy will still be encouraged to attend Month 12 visit (see Section 4.2).

A composite endpoint is defined so that a %CfB value of zero is taken for anyone who dies. The primary analysis assumes any missing data are MAR and the robustness of this assumption explored in sensitivity analyses (see Section 7.6.3.2). Reasons for discontinuation

of treatment will be collected as far as possible so that sensitivity analysis can take account of reasons related to treatment or osteoporosis differently to those unrelated.

Where a hypothetical strategy is taken in the estimand, data will be excluded after the first occurrence of ICE (eg, missing a dose, errors or deviations in dosing or receipt of any prohibited therapies or other osteoporosis medication for Estimand 1a) and treated as missing.

7.8 Interim Analyses

There will be two main analysis points after each study period is complete:

- Main Treatment Period: Analyses include data after all subjects have received the Month 12 assessments (prior to the third administration of study drug) or have terminated the study before Month 12. Analyses in the Clinical Study Report will include all data up to and including the Month 12 visit.
- Transition Period: Analyses up to Transition Period Month 6 will be reported in a Clinical Study Addendum after all subjects have completed all final assessments and the complete database is locked.

The statistical and programming team will be unblinded after the database is locked up to Month 12. An unblinding plan will give full details.

7.9 External Data Monitoring Committee

This study will be monitored by a committee of independent experts consisting of a PK specialist, statistician, chairing physician and independent physician. The DSMB will review and evaluate accumulating unblinded safety data to ensure the safety of study subjects and also review study results. The DSMB will communicate safety concerns and recommendations regarding study modifications or termination to mAbxience at any time during the conduct of the study. This decision will be based on benefit-risk evaluation. Records of all meetings will be archived. Further details will be provided in the independent DSMB charter.

8 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management. mAbxience assumes accountability for actions delegated to other individuals (eg, contract research organisations).

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports or ECG strips, etc.

All eCRF information is to be filled in. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

Investigative site personnel will enter subject data into Medidata Rave. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable PPD's standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary and concomitant medications will be coded using WHODRUG Global.

9 Ethics

9.1 Independent Ethics Committee or Research Ethics Committee

Federal regulations and the ICH guidelines require that approval be obtained from an IEC/REC before human subjects participate in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IEC/REC. Documentation of all IEC/REC approvals and of the IEC/REC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the site and will be available for review by mAbxience or its designee.

All IEC/REC approvals should be signed by the IEC/REC chairman or designee and must identify the IEC/REC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favourable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IEC/REC. The investigator must promptly supply mAbxience or its designee, the IEC/REC and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

9.3 Subject Information and Consent

A written informed consent in compliance with ICH and regulatory authority regulations will be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by mAbxience to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by mAbxience or its designee or both before IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IEC for review and approval before the start of

the study. If the ICF is revised during the course of the study, all active subjects must be reconsented by signing the revised form.

Before recruitment and enrolment, each prospective subject will be given a full explanation of the study, be allowed to read the approved ICF, and have any questions answered. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the ICF. The authorised person obtaining the informed consent also signs the ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research (if applicable) and explain/address the exploratory research portion of the study. Subject medical records need to state that written informed consent was obtained.

The investigator will retain the signed original ICF(s) and give a copy of the signed original form to the subject.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IEC/REC but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring and auditing by mAbxience, its designee, the FDA or the IEC/REC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from mAbxience or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Data Protection

All personal data collected related to subjects, Investigators or any person involved in the study, which may be included in mAbxience's databases, will be treated in accordance with local data protection law.

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

10.3 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow mAbxience to submit the complete and accurate certification or disclosure statements as required to the appropriate regulatory authorities. In addition, the investigator must provide to mAbxience a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither mAbxience nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither mAbxience nor PPD is financially responsible for further treatment of the subject's disease.

10.4 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 by providing all essential documents.

10.5 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

The investigator agrees to submit reports of serious adverse events to mAbxience and/or IEC/REC according to the timeline and method outlined in the protocol Section 6.5.1.4. In addition, the investigator agrees to submit annual reports to the study site IEC/REC as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IEC/REC with a summary of the study's outcome and mAbxience and regulatory authority(ies) with any reports required.

10.8 Records Retention

Essential documents should be retained until at least 15 years after the end of the study. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with mAbxience. It is the

responsibility of mAbxience to inform the investigator/institution as to when these documents no longer need to be retained. No records may be transferred to another location or party without written notification to mAbxience. No records may be destroyed during the retention period without prior written approval of mAbxience.

10.9 Publications and Results Disclosures

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, mAbxience will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. mAbxience has final approval authority over all such issues.

Data are the property of mAbxience and cannot be published without prior authorisation from mAbxience, but data and publication thereof will not be unduly withheld.

11 Study Management

The study administrative structure will include mAbxience, PPD, DSMB, third party vendors and central and local laboratories.

11.1 Monitoring

11.1.1 Monitoring of the Study

This study will be monitored according to an approved monitoring plan based on the objectives, purpose, design and complexity of the study. The investigator will allocate adequate time for all monitoring visits and between visits to facilitate the requirements of the study and study timelines. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given direct access to all study-related documents and study-related facilities (eg, pharmacy, diagnostic laboratory), phone, fax and internet and has adequate space to conduct the monitoring visit. Site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the study uses high quality data collection processes. The monitor will evaluate study processes based on PPD or designee standards, ICH E6 and all applicable regulatory guidelines. The mitigation plan for situations where monitoring visits cannot be conducted due to the ongoing COVID-19 pandemic is provided in Appendix 13.3.

11.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IEC/REC review and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow mAbxience, representatives of mAbxience, or a regulatory agency *(*eg, FDA, EMA or other regulatory agency) access to all study records.

The investigator should promptly notify mAbxience and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to mAbxience.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in the required procedures defined in this protocol, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by mAbxience or designee. Amendments to the protocol (including emergency changes) must be submitted in writing to the investigator's IEC/REC, along with any applicable changes to the ICF, for approval before subjects can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by mAbxience and the IEC/REC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol or to local regulations or ICH GCP guidelines that may or may not result in a significant, additional risk to the subject or impacts the integrity of study data.

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard/safety risk to study subjects without prior IEC/REC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IEC/REC for review and approval, to mAbxience for agreement, and to the regulatory authorities, where required.

In order to keep deviations from the protocol to a minimum, the investigator and relevant site personnel will be trained in all aspects of study conduct by mAbxience or its representative. This training will occur either as part of the investigator meeting or site initiation. Ongoing training may also be performed throughout the study during routine site monitoring activities.

The relationship of the protocol deviation to COVID-19 will be captured.

11.3 Study Termination

Although mAbxience has every intention of completing the study, mAbxience reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (End of Study visit). mAbxience will not provide further medical care or support after the study is completed.

If the study is prematurely terminated or suspended, mAbxience or investigator will promptly inform the investigators, the IECs/RECs, the regulatory authorities and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator will promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

11.4 Final Report

Whether the study is completed or prematurely terminated, mAbxience will ensure that the final data are summarised and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). mAbxience will also ensure that the clinical study reports in marketing applications (as applicable) meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the Clinical Study Report. The investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the final report, mAbxience will provide the investigator with the summary of the study results. The investigator is encouraged to share a summary of the results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

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13 Appendices

13.1 Appendix: Schedule of Events

Table 13-1 Schedule of Events

Trial Period		**Main Treatment Period**							**Transition/Safety Follow-Up Period**			
Visit Number*	1	**2**	3	4	5	**6**	7	**8**	9	10	11	12
Visit Label	Screening	**Baseline**	D11	M1	M3	**M6**	M9	**M12 EOT**	TP D11	TP M1	TP M3	TP M6 EOS
Visit Day	-28 to -1	1	11	36	90	182	270	365	M12+10 days	M12 +5 weeks	456	547
Window (±days)			±3	±5	±7	±10	±10	±10	±3	±5	±10	±10
Written informed consent[a]	X											
Eligibility[b]	X	X										
Demography data	X											
Medical history	X	X[c]										
NYHA Functional Classification	X											
Lateral spine X-ray[d]	X											
HBV, HCV and HIV-1/HIV-2[e]	X											
SARS-CoV-2[f]	X	As required										
Follicle-stimulating hormone	X											
Randomisation[g]		X										
Physical examination[h]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs, weight, height and body mass index[i]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[j]	X	X			X	X		X			X	
Haematology[k]	X	X	X	X	X	X	X	X	X		X	X
Coagulation[l]	X	X				X		X			X	
Clinical chemistry[m]	X	X	X	X	X	X	X	X	X		X	X
Urinalysis[n]	X	X				X		X			X	
Drug administration[g]		X				X		X				
Hypersensitivity, allergic reaction, injection site reaction monitoring[o]		X				X		X				

Trial Period		**Main Treatment Period**							**Transition/Safety Follow-Up Period**			
Visit Number*	1	**2**	3	4	5	**6**	7	**8**	9	10	11	12
Visit Label	Screening	**Baseline**	D11	M1	M3	**M6**	M9	**M12 EOT**	TP D11	TP M1	TP M3	TP M6 EOS
Visit Day	-28 to -1	1	11	36	90	182	270	365	M12+10 days	M12 +5 weeks	456	547
Window (±days)			±3	±5	±7	±10	±10	±10	±3	±5	±10	±10
Vitamin D and calcium supplement administration		Daily										
Review of vitamin D and calcium intake			X	X	X	X	X	X	X	X	X	X
BMD assessed with DXA[p]	X					X		X				
Pharmacodynamics sCTX[q]		X	X	X	X	X		X	X	X	X	X
Pharmacokinetics[r]		X	X	X	X	X		X	X	X	X	X
Immunogenicity[s]		X	X	X	X	X		X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[t]	X	X	X	X	X	X	X	X	X	X	X	X
Radiography[u]	As required											

Abbreviations: 25-OH vitamin D, 25-hydroxy vitamin D; aPTT, activated partial thromboplastin time; BMD, bone mineral density; COVID-19, coronavirus disease 19; D, Day; DXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; EOS, end of study; EOT, end of treatment; HBV, hepatitis virus B; HCV, hepatitis virus C; HIV-1/HIV-2, human immunodeficiency virus subtypes 1 and 2; ICF, informed consent form; INR, International Normalised Ratio; M, month; NYHA, New York Heart Association; PD, pharmacodynamic(s); PK, pharmacokinetic(s); PT, prothrombin time; SARS-CoV-2, severe acute respiratory coronavirus 2; sCTX, serum carboxy-terminal telopeptide cross-linked type 1 collagen; TP, Transition Period.

* In the case when site visits are not possible or the subject does not wish to visit the site, remote visits (by means of phone calls or video calls) or home visits (as a last option) may be allowed for visits that do not include study drug administration or BMD assessments. Even if a study visit cannot be made, possible data will be continuously collected via a telephone call and during the next visit, if applicable. The investigator will keep following up with subjects regarding any safety issues (adverse events, concomitant medication) by telephone call before the subjects visit the study site. Note: All remote activities depend on site- and country-specific requirements.

a. Informed consent must be obtained before any study-related procedures are performed.

b. The inclusion and exclusion criteria will be checked at screening and confirmed at baseline.

c. Review medical history and ensure that the subject remains qualified for the study.

d. An X-ray of the lateral spine will be performed at screening. This assessment may be also performed as required for confirmation of suspected new vertebral fractures. Radiographs will be assessed by quantitative grading at a central imaging centre.

e. At the screening visit, subjects will be screened for HBV surface antigen, HCV antibody and HIV-1/HIV-2 antibody. If a positive surface antigen test result is obtained for hepatitis B, a confirmatory test is required. In the case of a positive HCV test, an HCV viral RNA load test will be performed as a confirmatory test. In the case of a positive HIV-1/HIV-2 test result, a confirmatory test will be performed. Hepatitis B virus, HCV and HIV-1/HIV-2 analyses will be performed at the central laboratory.
f. At the screening visit, a COVID-19 test will be performed. Subjects who have a COVID-19 infection will be allowed to be rescreened on the basis that they have a confirmatory negative COVID-19 test result and have completely recovered from COVID-19 before being entered into the study. In the case that a subject is required to be rescreened within 28 days of the initial screening no additional tests are required to be performed. In the case that the subject is required to be rescreened after 28 days from the initial screening, all screening procedures/tests are required to be repeated (with the exception of DXA scans performed at screening, which will have a validity period of 3 months, provided the investigator considers the data from the DXA scan to be relevant [ie, the same DXA instrument will be used for the study and data on total hip, femoral neck and lumbar spine are available]). In the event the investigator deems the DXA scan invalid, a repeat DXA scan should be performed for the subject who has been re-examined. Systematic COVID-19 screening tests will be performed locally based on the site guidelines and on the investigator's discretion throughout the study period. If COVID-19 is confirmed after randomisation, the investigator will discuss case-by-case with mAbxience and the medical monitor. If the subject has contact with COVID-19 infected patients within 14 days following any site visit, the investigator will re-assess the visit schedule following the site and/or local regulatory guidelines.
g. On Day 1, during the Main Treatment Period, all subjects will be randomised in a 2:1:1 ratio to receive MB09-MB09, Prolia-MB09 or Prolia-Prolia. Subjects will receive one subcutaneous injection (60 mg/mL) of study drug on Day 1 and at Month 6 and Month 12. At Month 12, after all efficacy and safety assessments have been performed, the subject will enter the Transition/Safety Follow-Up Period and will receive the third dose of study drug. Subjects assigned to the MB09-MB09 arm (Arm 1) will receive MB09 on Day 1, at Month 6 and at Month 12. Subjects assigned to the Prolia-MB09 arm (Arm 2) will receive EU-Prolia on Day 1 and at Month 6, and MB09 at Month 12. Subjects assigned to the Prolia-Prolia arm (Arm 3) will receive EU-Prolia on Day 1, at Month 6 and at Month 12. All subjects will be followed up to Transition Period Month 6.
h. A complete physical examination will be performed at the screening, baseline (Day 1), Month 6, Month 12 and Transition Period Month 6 (End of Study) visits. A symptom-specific physical examination will be performed for other visits.
i. Vital signs (including systolic and diastolic blood pressures, heart rate, respiratory rate and body temperature) will be measured after 5 minutes of rest (sitting) (once at predose and once at postdose for Day 1, Month 6 and Month 12 visits, and once for all other visits).
j. Subjects are required to rest in a supine position for at least 5 minutes prior to recording of 12-lead ECG.
k. Haematology tests include haemoglobin, haematocrit, red blood cell count, white blood cell count with differential count, absolute neutrophil count, lymphocyte count and platelet count.
l. Coagulation tests include INR and aPTT.
m. Clinical chemistry tests include albumin, albumin-adjusted total serum calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, chloride, total cholesterol, high-density lipoprotein cholesterol, creatine kinase, creatine kinase-myocardial band isoenzyme, creatine phosphokinase, creatinine, gamma-glutamyl transferase, glucose, lactate dehydrogenase, triglycerides, magnesium, phosphate, potassium, sodium, total bilirubin, direct bilirubin, total protein, uric acid, troponin I, thyroid-stimulating hormone, parathyroid hormone (intact) and serum 25-OH vitamin D. Clinical monitoring of albumin-adjusted total serum calcium, serum 25-OH vitamin D and mineral levels (magnesium, phosphate) will be performed. Any sign and symptoms of hypocalcaemia will be closely sought[redacted]

adequately treated at the investigator's discretion. Serum 25-OH vitamin D will be re-tested within the Screening Period. Clinical monitoring of albumin-adjusted total serum calcium levels is recommended before each dose of study drug and in subjects predisposed to hypocalcaemia within two weeks after the initial dose of study drug. If any subject presents with suspected symptoms of hypocalcaemia during study drug treatment, albumin-adjusted total serum calcium levels should be measured during an unscheduled visit. After each administration of study drug at Day 1 and Month 12, albumin-adjusted total serum calcium levels will be monitored as part of the clinical chemistry panel on Day 11 and Transition Period Day 11, respectively. Note: Serum 25-OH vitamin D levels will also be measured at the unscheduled visit, if required.

n. Urinalysis tests include colour, pH, specific gravity, glucose, ketones, leukocytes, nitrite, protein, bilirubin, urobilinogen, occult blood and microscopic examination (only if urinalysis dipstick results are abnormal).

o. Subjects will be closely monitored by the investigator and/or subinvestigator for signs of injection site reactions or hypersensitivity/allergic reactions during the administration of the study drug and up to 1 hour (±10 minutes) after the administration of study drug. Vital signs including blood pressure, heart and respiratory rates and temperature (within 15 minutes prior to and at 1 hour ± 10 minutes after every injection) to monitor for possible hypersensitivity reactions. Hypersensitivity/allergic reactions will be also monitored by routine continuous clinical monitoring, including subject-reported signs and symptoms. Study drug will be administered at a location with immediate access to emergency support. The clinical team at the site facility should be prepared and qualified to conduct emergency care. In the case of anaphylaxis, the investigator must follow national and/or international recommendations of the specific treatment. Anaphylaxis with necessary therapeutic interventions will be reported as serious adverse events. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids and respiratory support including inhalational therapy, oxygen and artificial ventilation must be available and any types of ECG can be performed. Injection site reactions will be assessed 1 hour (±10 minutes) after the end of administration of the study drug. In the case that the subject experiences an adverse event on the day of study drug administration, they are to call the site or get immediate help.

p. Bone mineral density will be assessed by DXA at screening, and at Month 6 and Month 12, using validated instruments. Assessment of lumbar spine, total hip and femoral neck BMD assessments will be performed using the same DXA instrument for each subject throughout the study period. Note: The screening BMD assessment will be taken as the baseline BMD assessment. Note: A DXA scan taken up to 3 months of the screening DXA scan will be accepted as a rescreening DXA scan, provided the investigator considers the data from the DXA scan to be relevant (ie, the same DXA instrument will be used for the study and that data on total hip, femoral neck and lumbar spine are available). In the event the investigator deems the DXA scan invalid, a repeat DXA scan should be performed for the subject who has been re-examined.

q. Samples for PD testing (sCTX) will be taken in the morning after fasting overnight for 8 hours prior to assessment, and the subjects have to refrain from intense exercise the day prior to PD assessment. During the Main Treatment Period, PD assessments will be performed on Day 1 (0 predose), Day 11 and at Month 1, Month 3, Month 6 (predose) and Month 12 (for those subjects entering the Transition Period, this sample should be taken prior to the third dose of the study drug). During the Transition/Safety Follow-Up Period, PD assessments will be performed at Month 12 (predose) and 10 days, 5 weeks, 3 months and 6 months after the administration of the third dose of study drug (ie, Transition Period Day 11, Transition Period Month 1, Transition Period Month 3 and Transition Period Month 6).

r. Samples for PK testing will be collected up to 30 minutes prior to dosing of the study drug. Other samples may be taken at any time during a scheduled visit. During the Main Treatment Period, PK assessments will be performed on Day 1 (0 predose), Day 11 and at Month 1, Month 3, Month 6 (predose) and Month 12 (for those subjects entering the Transition Period, this sample should be taken prior to the third dose of the study drug). During the Transition/Safety Follow-Up Period, PK assessments will be performed at Month 12 (predose) and 10 days, 5 weeks, 3 months

and 6 months after the administration of the third dose of study drug (ie, Transition Period Day 11, Transition Period Month 1, Transition Period Month 3 and Transition Period Month 6).

s. Samples for immunogenicity testing will be collected up to 30 minutes prior to dosing of the study drug. Other samples may be taken at any time during a scheduled visit. Immunogenicity (antidrug antibody and neutralising antibody) will be performed on Day 1 (0 predose), Day 11 and at Month 1, Month 3, Month 6 (predose) and Month 12 (for those subjects entering the Transition Period, this sample should be taken prior to the third dose of the study drug) during the Main Treatment Period. During the Transition/Safety Follow-Up Period, immunogenicity assessments will be performed at Month 12 (predose) and 10 days, 5 weeks, 3 months and 6 months after the administration of the third dose of study drug (ie, Transition Period Day 11, Transition Period Month 1, Transition Period Month 3 and Transition Period Month 6). If any additional immunogenicity samples are required to be taken if immune-related adverse events occur, the investigator is to seek prior advice from PPD medical monitor and mAbxience before performing the additional sampling.

t. Adverse events will be assessed from the date that the ICF is signed until the End of Study visit (Transition Period Month 6 visit), regardless of the relationship to the study drug. The related adverse events will be followed until resolution or improvement to baseline, relationship reassessed as unrelated, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure.

u. Lateral spine radiographs will be performed at screening only (per footnote d). Radiographs will be performed only as required for confirmation of suspected new clinical fractures. Radiographs will be assessed by quantitative grading at a central imaging

13.2 Appendix: New York Heart Association Functional Classification

As defined in Raphael et al 2007, the NYHA classification is used in subjects with heart failure.

Class	Symptoms
I (Mild)	Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or anginal pain.
II (Mild)	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain.
III (Moderate)	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea, or anginal pain.
IV (Severe)	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

13.3 Appendix: Risk Assessment and Mitigation Plan due to COVID-19

The novel SARS-CoV-2 was initially identified during an outbreak of atypical viral pneumonia cases of unknown cause in the People's Republic of China in December 2019 and the disease caused by SARS-CoV-2 has been designated as COVID-19. On 12 March 2020, the WHO declared the SARS-CoV-2 infection outbreak a global pandemic and to date (12 July 2021) in excess of 4.0 million deaths have been reported globally (WHO COVID-19 Dashboard 2021).

Due to the global impact of the COVID-19 pandemic, mAbxience and PPD are taking proactive measures to guarantee that all study site staff and subjects involved in the study are secure and the subjects remain in the study until their last visit, with continuation of treatment during the study period.

13.3.1 Benefit and Risk Assessment on Study Population

Considering the most common symptoms of COVID-19 are fever, dry cough, and tiredness (WHO Q&A on COVID-19) and the irrelevance between cause of COVID-19 and osteoporosis disease itself, osteoporosis symptoms and disease itself have a low chance to deteriorate directly due to COVID-19. Furthermore, no high risk was seen for COVID-19 complications in women older than 50 years for postmenopausal or aromatase inhibitor-induced osteoporosis, and the subjects are recommended to maintain the denosumab treatment for the management of osteoporosis during the COVID-19 outbreak (Gittoes et al 2020). However, the relevance cannot be excluded since no studies have been conducted and there have been a few research studies reporting the increased risk for respiratory infections following denosumab treatment (Formenti et al 2011).

Moreover, it has yet to be concluded that calcium and vitamin D, which is a protocol-defined co-administration, may have beneficial effects on COVID-19. To date, it has been shown that the subjects with osteoporosis may be protected from SARS-CoV-2 by vitamin D independently of the pharmacologic antiosteoporotic treatments (Bilezikian et al 2020).

Quarantine of COVID-19 positive subjects will be carried out based on the standard of care of each study site and/or local regulatory guidelines. Taking all these facts into consideration, the risks of COVID-19 infection for each subject are not expected to increase by participating in this study. Yet due to the possibility of increasing the safety risk by being involved in the

study, a systematic risk assessment will be conducted during the study by mAbxience and PPD through a sufficient discussion with the investigators. At the screening visit, a COVID-19 test will be performed. Subjects who have a COVID-19 infection will be allowed to be rescreened on the basis that they have a confirmatory negative COVID-19 test result and have completely recovered from COVID-19 before being entered into the study. In the case that a subject is required to be rescreened within 28 days of the initial screening, no additional tests are required to be performed. In the case that a subject is required to be rescreened after 28 days from the initial screening, all screening procedures/tests are required to be repeated (with the exception of DXA scans performed at screening, which will have a validity period of 3 months, provided the investigator considers the data from the DXA scan to be relevant [ie, the same DXA instrument will be used for the study and data on total hip, femoral neck and lumbar spine are available]). In the event the investigator deems the DXA scan invalid, a repeat DXA scan should be performed for the subject who has been re-examined. Systematic COVID-19 screening tests will be performed locally based on the site guidelines and on the investigator's discretion throughout the study period. If COVID-19 is confirmed after randomisation, the investigator will discuss case-by-case with mAbxience and the medical monitor. If the subject has contact with COVID-19 infected patients within 14 days following any site visit, the investigator will re-assess the visit schedule following the site and/or local regulatory guidelines.

13.3.2 Mitigation Plans

13.3.2.1 Informed Consent

Due to COVID-19 restrictions, oral informed consent may be obtained by the phone and supplemented with an e-mail confirmation. Then, normal consent procedures will be applied as soon as subjects can visit the site.

13.3.2.2 Study Drug Management

To cope better with the sudden imposition of movement restriction and/or increased shipment lead time due to frequent flight cancellation and limited staff at customs, sufficient study drug will be supplied to cover subject visits for longer periods. Inter-country study drug transfer using regional airways will be considered in case intercontinental flights are repeatedly cancelled. In addition, PPD Global Clinical Supplies will prepare site-to-site transfer of study drug from nearby clinical study sites in case an agile resupply is required

(eg, more subjects are enrolled at a study site than anticipated but additional supplied study drug is not sufficient to meet demand).

13.3.2.3 Rescheduling of Visit and Study Drug Administration Schedule of Subjects

The COVID-19 screening tests will be performed locally based on each study site and/or local regulatory guidelines upon the investigator's discretion throughout the study period. If COVID-19 is confirmed positive during the Screening Period, the subject will not be enrolled in this study until confirmation of complete recovery from COVID-19 as per study site and/or local regulatory guidelines. Although subjects can be screened only once under normal circumstances as specified in Section 4.1.4, additional rescreening can be performed only in limited cases considering COVID-19. If COVID-19 is confirmed after randomisation, the investigators will discuss on a case-by-case basis regarding the specific case of the subject with mAbxience. In the case that a subject is required to be rescreened within 28 days of the initial screening, no additional tests are required to be performed. In the case, that the subject is required to be rescreened after 28 days from the initial screening, all screening procedures/tests are required to be repeated (with the exception of DXA scans performed at screening, which will have a validity period of 3 months, provided the investigator considers the data from the DXA scan to be relevant [ie, the same DXA instrument will be used for the study and data on total hip, femoral neck and lumbar spine are available]). In the event the investigator deems the DXA scan invalid, a repeat DXA scan should be performed for the subject who has been re-examined. In the case of a subject who has contact with COVID-19 infected patients within 14 days of screening, the subject will not be enrolled in the study. If the subject has contact with COVID-19 infected patients within 14 days following any study site visit, the investigator will re-assess the visit schedule following the study site and/or local regulatory guidelines.

Investigators will promptly notify mAbxience if any unfavourable situation has occurred in relation to local COVID-19 status (eg, study site shut down, lock down of city, cohort isolation, etc). For study sites where the subjects are unable to travel or use public transportation, mAbxience will support the subjects with alternative transportation or reimbursement for travel to ensure the visits can be made within the window or the visit can proceed at the earliest possible opportunity. Pre-approval is required for reimbursement.

The subjects require face-to-face interactions for study drug administration. Therefore, in the event subjects cannot visit the study site on the scheduled day for injection, the treatment schedule will be adjusted following Section 5.7. However, if study drug administration cannot be carried out within an allowed visit window (Appendix 13.1) or a missed dose is expected, whether to continue with the subsequent study drug will be discussed with mAbxience, ensuring the compliance with the study protocol to such an extent that an ongoing benefit-risk assessment for the clinical study and subjects is still possible.

In the case when site visits are not possible or the subject does not wish to visit the site, remote visits (by means of phone calls or video calls) or home visits (as a last option) may be allowed for visits that do not include study drug administration or BMD assessments. Study nurses will be allowed to conduct home visits in order to collect blood samples from the subject. Even if a study visit cannot be made, possible data will be continuously collected via a telephone call and during the next visit, if applicable. The investigator will keep following up with subjects regarding any safety issues (adverse events, concomitant medication) by telephone call before the subjects visit the study site. Note: All remote activities depend on site- and country-specific requirements.

Although the COVID-19 pandemic situation is likely to introduce more protocol deviations than under normal circumstances, protocol deviations will be managed in accordance with the standard procedures. The number and type of deviations will be monitored periodically to assess whether a protocol amendment or other modifications are needed. In addition, if local COVID-19 travel restrictions are enacted making study site visits difficult or impossible, alternative options may need to be considered.

13.3.2.4 Monitoring of Visits

Whenever possible, clinical research monitors will continue to conduct on-site monitoring visits per current clinical management plan. If a monitor is unable to travel for an on-site monitoring visit (eg, local lockdown/travel restriction) or if a site is unable to accommodate a monitor for an on-site visit, then a remote monitoring visit will be conducted where approved by site policies, regulatory permitted and in accordance with the clinical management plan. Follow-up measurements will be implemented when the situation is normalised, including on-site monitoring for a period that is sufficient to ensure the impact of the reduced monitoring can be rectified and problems resolved or properly documented. Data subject to remote source data verification are likely to require re-monitoring, in particular if it was

based on pseudonymised documents, which cannot be considered as source documents, and considering that remote monitoring is expected to have focused on the most critical information. An on-site monitoring visit will be performed at a later date as soon as possible.

In the cases where subjects are not able to attend study visits due to the presence of a SARS-CoV-2 infection, the investigator will discuss with mAbxience potential mitigation approaches (including but not limited to extending the visit windows, conducting evaluations via a video link or phone call, allowing for safety procedures to be performed at a local facility).

For the duration of special circumstances, the following measures may be implemented for enrolled subjects:

- Visits may take place in a different location than defined in the protocol. If this is not feasible, then the visit may take place virtually with documentation of the means of communication (eg, phone call or video conference).
- Biological samples may be collected and analysed at a different location than defined in the protocol. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until shipping/processing.
- If it is not possible to collect the biological samples or safety assessments (eg, vital signs) within the predefined interval in the protocol then the interval may be extended up to a maximum duration of 14 days.
- If a safety assessment cannot be performed within the modified window, the investigator must review the benefit-risk for the subject continuation in the study and record this in the medical records.
- The rationale (eg, the specific reasons behind the changes) and the outcome of the discussion with the medical monitor will be documented in the medical record. Information on how each visit was performed will be recorded in the eCRF.

Video review of medical records with clinical site team must take place without sending any copy to the monitor and without the monitor recording images during the review. The sites, mAbxience and PPD must have processes in place to ensure the subjects' privacy.

The recording of remote monitoring visits, emailing or faxing of any subject data even anonymised) or discussions are strictly prohibited.

13.3.2.5 COVID-19 Vaccine and Other Vaccinations

The study indication, study drug and assessments are not expected to be impacted by vaccination. However, COVID-19 vaccination within 14 days prior to randomisation to study drug administration or 14 days prior to study drug administration at Month 6 or Month 12 is prohibited. The use of other required vaccines is not prohibited/excluded in this study.

13.3.2.6 DXA Scan and X-Ray Assessments

For BMD assessment, only validated bone densitometers will be allowed during the study, and the same DXA instrument will be used for all study procedures for each subject during the study. However, in COVID-19 pandemic situation, if the subjects are restricted in their ability to travel to the study sites and/or the study sites are locked down, alternative imaging centres can be considered to acquire the DXA scans. The alternative centre will follow the central imaging provider's guidance on selecting an appropriate replacement scanner and a phantom scanning process to quantify any calibration differences. All DXA scans will be submitted to and analysed by the central imaging vendor.

For vertebral fractures, the lateral spine X-ray will be performed in cases of suspected new fractures during the study and may be performed in the alternative imaging centres in COVID-19 pandemic situation (study site shutdown, lockdown of city etc). The lateral spine X-ray for vertebral fracture as well as copies of other diagnostic image and related source documents will be submitted to the central imaging vendor for confirmation of fracture. If X-ray is necessary to support the subject's medical care, the X-rays also could be read locally.

13.3.2.7 Study Site Monitoring and Audit

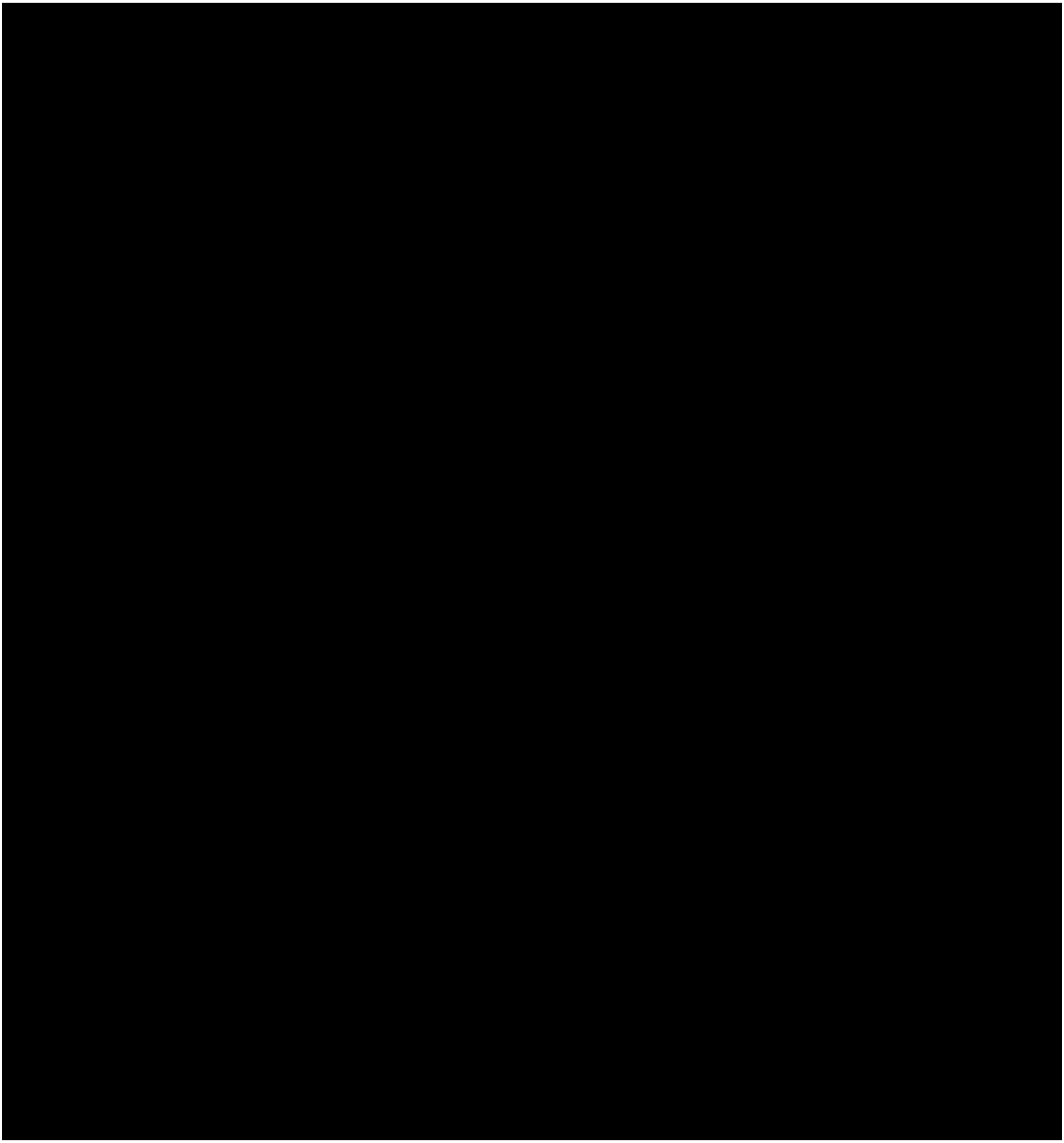
In cases where a monitoring visit cannot be performed because of the prevailing COVID-19 situation, centralised monitoring will be performed by mAbxience and/or PPD as alternatives, particularly, for the study sites where the first subject has been randomised but the first monitoring visit has not been performed. Manual data review in the eCRF will be performed and if any mistakes or deviations are observed, proper guidance will be provided to prevent them happening in the future. mAbxience and/or PPD will review the data entered

in the eCRF continuously and ensure queries are raised and support the study sites as necessary. If necessary, mAbxience will create and review a report based in the eCRF data to check whether visits, assessments and administrations of study drug are in progress according to protocol and the same will be shared with PPD for study site management.

Audits are required to ensure quality assurance throughout the study period in order to evaluate study conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements. In cases where an audit cannot be performed due to the COVID-19 pandemic situation, mAbxience will postpone audits or consider performing remote audits after careful consideration of the COVID-19 pandemic situation according to guidance on the management of clinical studies during the COVID-19 (coronavirus) Pandemic (EMA 2020). Audits will be conducted only when permitted under national, local and/or organisational social distancing restrictions.

13.3.2.8 Handling of Missing Data

To assess any possible risks on data collection, data will be routinely reviewed according to centralised monitoring plan and risk-based monitoring plan. After data collection, missing data on the primary efficacy analysis due to COVID-19 will be analysed as specified in Section 7.7 with other missing cases. However, if a different approach is required for missing data due to COVID-19, it will be discussed at the blinded data review meeting on a case-by-case basis and the procedure for handling missing data in the statistical analysis will be specified in the statistical analysis plan.



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